ISOLAGEN THERAPY™ (LAVIV™)

Autologous Cell Therapy

Cellular, Tissue, and Gene Therapies Advisory Committee
Briefing Document

Meeting Date: October 09, 2009

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Date : September 09, 2009

Advisory Committee Briefing Materials: Available for Public Release

EXECUTIVE SUMMARY

INTRODUCTION TO ISOLAGEN THERAPY™ (LAVIV™)

Isolagen Therapy™ (Laviv™) is an autologous cell therapy product composed of a suspension of cultured fibroblasts derived from the patient's own skin. The cultured fibroblasts in the Isolagen Therapy™ Drug Product are viable, replication competent cells that are confirmed to contain collagen *in vitro.* The cells are injected intradermally at the intended treatment site. Following injection, the cultured fibroblasts are thought to synthesize new extracellular matrix and/or to stimulate the remodeling of existing tissue components, thereby altering the structure, texture and appearance of the skin at the site of injection. Isolagen Technologies, Inc. (Isolagen) is developing Isolagen Therapy™ for a number of aesthetic and therapeutic indications. The first proposed indication for licensure of Isolagen Therapy™ is for cosmetic use to improve the appearance of moderate to severe nasolabial fold wrinkles.

Isolagen Therapy™ is a biologic Drug Product, or somatic cell therapy, that is distinct in composition and mechanism of action from currently marketed dermal filler products for the treatment of facial rhytids. Dermal fillers are widely employed by plastic surgeons and dermatologists to temporarily correct the appearance of nasolabial fold wrinkles and other facial rhytids. These products, containing collagen, hyaluronic acid, or other polymeric substances, achieve wrinkle correction through a space-filling effect at the site of injection. Although newer generation products have achieved a longer duration of effect and a reduced risk of hypersensitivity reactions compared to the early collagen-based fillers, the polymers within all fillers naturally degrade over time and are not replenished. Thus, wrinkle correction is temporary and re-treatment is necessary to maintain the desired appearance. In contrast, Isolagen Therapy™ provides wrinkle correction through a biological mechanism employing the patient's own cells to modify the microstructure of the skin at the site of injection. Although the exact mechanism of action is not known, it is believed that the injected fibroblasts deposit new extracellular matrix proteins and/or stimulate the remodeling of existing tissue components of the dermis. Thus, the onset of Isolagen Therapy™ effect is not immediate but develops over a period of weeks, and the duration of effect is potentially long-lasting.

MANUFACTURE OF ISOLAGEN THERAPY™

Isolagen Therapy™ is manufactured by propagation and expansion of dermal fibroblasts obtained from a small biopsy of the patient's skin. Three 3-mm punch biopsies are collected by the treating physician from behind the ear, where the skin is likely to have received less sun exposure and where there are fewer concerns associated with possible scarring due to biopsy. The tissue is shipped in sterile phosphate buffered saline to Isolagen's manufacturing facility, where it is briefly digested with enzymes to release the cells, which are then seeded into a tissue culture vessel. The cells are serially passaged over a period of weeks to obtain a quantity sufficient for treatment, then cryopreserved until the patient can be scheduled for administration of Isolagen Therapy™. The Drug Product for patient injection is prepared one day prior to each scheduled day of treatment, by thawing and washing a portion of the cryopreserved cells, and resuspending them at

the appropriate concentration for injection. The Isolagen Therapy™ Drug Product is shipped for overnight delivery to the clinic and must be administered within 48 hours of product release.

REGULATORY HISTORY AND CLINICAL DEVELOPMENT OVERVIEW

Isolagen Therapy™ was sold commercially in the United States (U.S.) as a cosmetic treatment from December 1995 to February 1999. Discussion regarding the previous commercial experience is included in published literature (Boss et al. 2000a and 2000b, West and Alster 1998, and Watson et al. 1999). Isolagen Therapy™ was also sold with limited distribution in the United Kingdom (U.K.) from 2002 to 2007 and in Australia from 2003 to 2004. Isolagen discontinued marketing of Isolagen Therapy™ in the U.S. in February 1999 when the FDA required all somatic cell therapies to file Investigational New Drug (IND) applications and follow a formal approval process. Isolagen initiated U.S. clinical trials of Isolagen Therapy™ under IND in 2003. Over 6,000 patients were treated with Isolagen Therapy™ in the U.K. Over 1,200 patients were treated in the U.S. prior to the submission of the IND, and 508 subjects have been treated under U.S. IND.

Isolagen Therapy™ has been tested for the treatment of facial wrinkles and creases in two Phase II studies and five Phase III studies (see Table 2 of this document; Weiss et al. 2007). Studies IT-R-005 (N=175) and IT-R-006 (N=197) are the pivotal clinical trials submitted in support of product licensure for the treatment of moderate to severe nasolabial fold wrinkles in adults ≥ 18 years of age. The earliest trials, IT-R-001 (N=40) and IT-R-002 (N=151), provided exploratory data that guided the design of the subsequent, larger-scale, Phase III studies. Studies IT-R-003A (N=107) and IT-R-003B (N=106) provide robust, well-controlled data supporting the efficacy and safety of Isolagen Therapy™ for the treatment of facial contour deformities. Finally, study IT-R-007 (N=45) provides additional data in support of the safety of Isolagen Therapy™ administration to the face.

EFFICACY OF ISOLAGEN THERAPY™

The efficacy of Isolagen Therapy™ in the treatment of facial contour deformities, including facial wrinkles and scars, has been evaluated in multiple randomized, blinded, placebo-controlled clinical studies, as outlined above. The pivotal clinical studies submitted to the FDA in support of licensure of Isolagen Therapy™ are studies IT-R-005 and IT-R-006 which evaluated the efficacy of Isolagen Therapy™ in the treatment of moderate to severe nasolabial fold wrinkles.

The pivotal clinical trials, IT-R-005 and IT-R-006, were conducted under identical clinical protocols that were developed in coordination with the FDA under a Special Protocol Assessment (SPA), whereby the Agency agreed that the pivotal study design was adequate to provide the primary basis of an efficacy claim. The pivotal studies were multicenter, randomized (1:1 by site), placebo-controlled, double-blind studies. As appropriate for clinical indications that impact patient satisfaction, co-primary endpoints were evaluated. Subjects, according to inclusion criteria, were “dissatisfied” or “very dissatisfied” with the appearance of their nasolabial fold wrinkles and were scored as having moderate to severe nasolabial fold wrinkles by a blinded Evaluator. Subjects

were scheduled to receive either Isolagen Therapy™ or placebo in three treatments with an interval of five weeks (± one week) between treatments. The co-primary efficacy endpoints were based on the blinded Investigator's live assessment of nasolabial fold wrinkle severity and the subject's blinded live assessment of their satisfaction with the wrinkles on the lower part of the face compared to the respective Baseline assessments. Both endpoints were evaluated at six months following the third treatment visit for the primary efficacy analysis. Assessments were also performed at zero, two and four months after the third treatment visit for secondary analyses of efficacy.

Subjects were categorized as "responders" or "non-responders" based on the change from baseline in the subject and the Evaluator assessment scores. For the subject assessment scale, a 2-point improvement on a 5-point scale was required to be considered a responder. For the Evaluator assessment scale, a responder was defined as a 2-point improvement on a 6-point scale for *both* nasolabial fold wrinkles. The co-primary efficacy analyses of both pivotal studies compared the proportion of responders in the Isolagen Therapy™ and placebo treatment groups based on the Evaluator's wrinkle assessment and the subject's wrinkle assessment.

The primary efficacy results of the pivotal clinical trials, based on a 2-point improvement, are presented in the table below. In both pivotal studies, a higher proportion of responders was observed among Isolagen Therapy™-randomized subjects compared to placebo-randomized subjects on both the Evaluator and subject assessment scales, where all subjects with missing data were treated as non-responders. The differences in response rates between treatment groups were statistically significant in all cases, with p-values below 0.01 (see Table 10 in this document). Thus, the co-primary efficacy endpoints for each pivotal clinical study, as agreed upon under the SPA, were met. These data not only definitively demonstrate the treatment effect of Isolagen Therapy™ relative to placebo, but also the clinical effect of Isolagen Therapy™.

A number of secondary analyses were performed to assess the efficacy of Isolagen Therapy™ compared to placebo based on criteria that were deemed to be clinically meaningful for this population. The table below also presents the proportion of subjects from both pivotal studies who experienced a 1-point improvement on a 5-point scale for the subject assessment or on a 6-point scale for the Evaluator assessment, after receiving at least one dose of Isolagen Therapy™ or placebo. Assessments were performed at the final clinic visit, approximately 6 months after the third dose of treatment. A large proportion of Isolagen Therapy™-treated subjects experienced improvement in their wrinkles based on either the subjects' or the Evaluators' assessments. The difference in the proportion of responders in each treatment group was statistically significant.

Clinical Efficacy of Isolagen Therapy™ based on 1-Point and 2-Point Improvements on Wrinkle Assessment Scales in Both Pivotal Studies

	2-Point Improvement		1-Point Improvement	
	Isolagen Therapy™	**Placebo**	**Isolagen Therapy™**	**Placebo**
Subject Wrinkle Assessment				
Percent Responders	59%	26%	78%	48%
p-value	<0.0001[a]		<0.0001[a]	
Evaluator Wrinkle Assessment				
Percent Responders	30%	8%	64%	36%
p-value	<0.0001[a]		<0.0001[a]	

[a]Fisher's Exact test

In another analysis of clinical benefit, the proportion of subjects who experienced an improvement in their wrinkle appearance was determined based on the subject's or the Evaluator's comparison of photographs taken at Baseline and at six months after the third treatment. A large proportion of Isolagen Therapy™-treated subjects (67% based on the subject's assessment and 57% or 59% based on the Evaluator's assessment of the left and right nasolabial fold, respectively) achieved a positive response based on this analysis. The proportion of responders was higher among Isolagen Therapy™-treated subjects compared to placebo-treated subjects by a statistically significant margin ($p < 0.0001$ for the subject's assessment, and $p < 0.0001$ for the Evaluator's assessment, see Table 16 and Table 17, respectively).

The gradual onset of Isolagen Therapy™ effect was confirmed by the pivotal trial results in which the proportion of subjects responding to treatment increased from the first post-treatment assessment (after two treatments) through the last assessment (six months after the third treatment). The duration of Isolagen Therapy™ effect was not fully evaluated in the pivotal clinical trials because follow-up was not continued beyond six months after the last treatment. However, for the subjects who responded at the first assessment visit, a large majority (71%, subject's assessment; 61%, Evaluator's assessment) sustained their response through the 6-month duration of follow-up. Therefore, the duration of Isolagen Therapy™ effect is considered to be at least six months, and may be substantially longer for many subjects.

SAFETY OF ISOLAGEN THERAPY™

The safety of Isolagen Therapy™ was evaluated in the Integrated Safety Population, which included all subjects who received at least one dose of study treatment in all seven of the Phase II and Phase III clinical trials listed in Table 2 of this document. Safety results for 508 Isolagen Therapy™-treated subjects and 354 placebo-treated subjects were included in the analysis. Injection site reactions were by far the most commonly reported adverse events in the studies. The most frequent adverse events associated with treatment with Isolagen Therapy™ or placebo were injection site erythema (16%), injection site swelling (14%), injection site bruising (11%), injection site pain (6%), and

injection site edema (4%). Injection site reactions were slightly more frequent among Isolagen Therapy™-treated subjects than placebo-treated subjects. Injection site reactions were largely of mild or moderate intensity and of short duration. Infrequently, subjects reported injection site nodules (4%), papules (2%), or hemorrhage (3%). Other adverse events of particular interest are described in Section 6 of this briefing document.

There were no Serious Adverse Events or deaths during clinical trials of Isolagen Therapy™ that were considered related to study treatment, and adverse events of severe intensity were infrequent and generally resolved without sequelae. The safety data indicate that Isolagen Therapy™ is safe for the treatment of nasolabial fold wrinkles.

PROPOSED INDICATION AND BASIS FOR APPROVAL

The proposed indication statement for Isolagen Therapy™ is as follows:

> Isolagen Therapy™ is an autologous cell therapy indicated for the treatment of moderate to severe nasolabial fold wrinkles in adults ≥ 18 years of age.

The safety of Isolagen Therapy™ has been demonstrated based on the integrated results from seven clinical trials, wherein the observed adverse effects of treatment were primarily limited to reactions at the site of injection, and were of short duration. Long-term (12 month) follow-up of the pivotal study population has confirmed the safety of Isolagen Therapy™ and no additional safety issues emerged at 12 months.

The efficacy of Isolagen Therapy™ in improving the appearance of nasolabial fold wrinkles has been established in multiple clinical studies, based on the assessments of blinded Evaluators and the study subjects. In each of two pivotal clinical trials, the co-primary efficacy endpoints developed in coordination with the FDA under SPA were both met, establishing the efficacy of Isolagen Therapy™ for the improvement of moderate to severe nasolabial folds.

Isolagen Therapy™ represents a novel treatment for nasolabial fold wrinkles based on a unique, biological mechanism that is intended to have a gradual onset and longer duration of effect than currently marketed dermal filler products.

COMPANY AND PRODUCT NAME CHANGES

Isolagen Technologies, Inc. is in the process of legally changing the company name to Fibrocell Technologies, Inc. At the time this briefing package was submitted, the product name Laviv™ was in the process of being submitted to FDA for approval to replace Isolagen Therapy™. For ease of review purposes and consistency with the FDA briefing package for the advisory committee meeting, the company name Isolagen Technologies, Inc. (Isolagen) and the product name Isolagen Therapy™ are used throughout this document.

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LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event – An adverse event (AE) is any adverse change in health or "side-effect" that occurs in a person who participates in a clinical trial while the patient is receiving the treatment (study medication, application of the study device, etc.) or within a pre-specified period of time after their treatment has been completed.
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance statistical test
ASAPS	The American Society of Aesthetic Plastic Surgery
BLA	Biologics License Application - The formal application by which pharmaceutical companies request FDA permission to commercially market and sell a biologic product.
BSA	Bovine serum albumin
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CMC	Chemistry, manufacturing and controls
CMH	Cochran-Mantel-Haenszel
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CTD	Common Technical Document
CTGTAC	Cellular, Tissue, and Gene Therapies Advisory Committee
DMEM	Dulbecco's Modified Eagle's Medium
DVD	Digital versatile disc
FBS	Fetal bovine serum
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IND	Investigational New Drug application - The application to the FDA that allows a company to test potential new drugs and biologics in humans.
ITT	Intent to treat
MITT	Modified intent to treat
MoA	Mechanism of Action – The way a clinical therapy works in the body to provide its beneficial effect.
NLF	Nasolabial fold – The two lines or skin folds that run from each side of the nose to the corners of the mouth. They separate the cheeks from the upper lip.

PBS	Phosphate buffered saline
PVP	Pharmacovigilance plan
QA	Quality assurance
QC	Quality control
SAE	Serious adverse event
SD	Standard deviation
SOC	Systems organ class
SOP	Standard operating procedure
SPA	Special Protocol Assessment
TEAE	Treatment emergent adverse event
USP	United States Pharmacopeia
VAS	Visual analog scale

1. INTRODUCTION TO ISOLAGEN THERAPY™

Isolagen Therapy™ (Laviv™) is an autologous cell therapy product composed of a suspension of cultured fibroblasts derived from the patient's own skin. The cultured fibroblasts in the Isolagen Therapy™ Drug Product are viable, replication competent cells that are confirmed to contain collagen *in vitro.* The cells are injected intradermally at the intended treatment site. Following injection, the cultured fibroblasts are thought to synthesize new extracellular matrix, or to stimulate the reorganization of existing tissue components of the dermis, thereby altering the structure, texture and appearance of the skin at the site of injection. Isolagen Technologies, Inc. (Isolagen) is developing Isolagen Therapy™ for a number of clinical indications, including the treatment of facial wrinkles, acne scars, restrictive burn scars, vocal cord scars and gingival recessions. The first proposed indication for licensure of Isolagen Therapy™ is for cosmetic use to improve the appearance of moderate to severe nasolabial fold wrinkles (the two lines or skin folds that run from each side of the nose to the corners of the mouth). This briefing document summarizes the clinical development of Isolagen Therapy™ for this indication, with particular emphasis on the results from controlled clinical trials that demonstrate the safety and efficacy of Isolagen Therapy™ in the intended patient population.

1.1. PRODUCT DESCRIPTION

Manufacture of Isolagen Therapy™ is initiated by collection of a skin biopsy from the patient seeking treatment. Skin tissue (dermis and epidermis layers) is biopsied from a patient's post-auricular area (behind the ear) and shipped in sterile buffer at 2-8°C via next day delivery to Isolagen's manufacturing facility in Exton, PA. Fibroblasts isolated from the tissue are expanded using standard cell culture techniques to a quantity sufficient for re-injection into the patient's target treatment area.

The Bulk Drug Substance consists of expanded autologous fibroblasts, formulated to the target cell concentration and cryopreserved in cryovials. The Drug Product consists of thawed and washed Drug Substance cells, resuspended to a concentration of 1.0 - 2.0 x 10^7 cells/mL in sterile medium. The Drug Product is filled into 2 mL polypropylene cryovials, to contain 1.2 mL cell suspension, and shipped immediately at 2-8°C to the clinical site. The Drug Product is stable at 2-8°C for up to 48 hours prior to injection.

1.2. RATIONALE FOR PRODUCT DEVELOPMENT

The skin is composed of three major structural and functional layers: the epidermis, the dermis, and the subcutis. The epidermis is the outermost layer of the skin that provides an impermeable barrier to the environment and a first line of defense against pathogenic organisms. Underlying the epidermis is the dermis, which contains the blood and lymph vessels of the skin and the sensory nerve endings responsible for sensations for heat, cold, and pressure (Kanitakis 2002). The primary cell type found in the dermis is the fibroblast. Fibroblasts are loosely distributed throughout the dermis where they are responsible for manufacturing and organizing the components of the extracellular matrix,

such as collagen and elastin, that provide the skin with strength and elasticity. Fibroblasts also play a critical role in wound healing responses.

The aging of skin occurs as a result of intrinsic and extrinsic factors. Intrinsic aging is a naturally occurring process of slow tissue degeneration, while extrinsic aging occurs as a result of environmental influences that independently have degenerative effects on the skin. Extrinsic factors include sun damage, pollution, nicotine, repetitive muscle movements, diet, sleeping position, and overall health (Farage 2008).

With increasing age, the thickness of the dermis declines, with a generalized decrease in blood vessels, fibroblasts and other cell types. Microscopic evaluation of aged skin tissue reveals a decrease in the quantity of collagen fibrils (Lovell 1987), an apparent "unraveling" of the collagen bundles, and a compaction of the fibrous components due to a loss of space between the fibers (Lavker 1987, Lavker 1989). Collagen expression levels are significantly lower in aged skin compared to younger skin (Uitto 1989). The precise mechanism by which these alterations in skin structure lead to the visible signs of aging (wrinkles, skin slackness and sagging) are not fully understood; however, it is assumed that the observed decline in collagen content and biosynthesis, disorganization, compaction and degradation of collagen fibers, loss of elastic microfibrils and accumulation of elastic material, in addition to other structural changes, are causally related to the appearance of skin wrinkles (Bhawan 1998).

The rationale underlying Isolagen Therapy™ is to reinvigorate the microscopic structure of the skin through a biological mechanism, specifically, by injecting living fibroblasts into the area of the skin where an improvement in the skin's appearance is desired. The autologous fibroblasts that comprise the active component of Isolagen Therapy™ are viable cells that are confirmed to contain collagen *in vitro.* Although the exact mechanism of action has not been confirmed, it is thought that intradermal injection of these cells into the superficial papillary dermis leads to an increase in the synthesis of extracellular matrix components such as collagen, and/or remodeling of the existing microstructure of the dermis, in the area of Isolagen Therapy™ injection. The effect of the therapy is not immediate, but instead provides a gradual improvement in the appearance of the treated area over time. Based on the biological mechanism of action, the duration of Isolagen Therapy™ effect is potentially long-lasting.

Isolagen Therapy™ has potential applicability in various indications where abnormal skin structure leads to cosmetic or functional pathology (e.g., acne scars or restrictive burn scars), and Isolagen has initiated clinical evaluation of the product in a number of these indications. The use of Isolagen Therapy™ for the treatment of facial contour deformities, including nasolabial fold wrinkles, is the most advanced clinical program, in part due to the extensive prior commercial experience in this indication (see Section 2.1). Isolagen is currently seeking licensure of Isolagen Therapy™ for the treatment of nasolabial fold wrinkles based on statistically significant clinical evidence of the efficacy and safety of the product for this use.

1.3. PROPOSED INDICATION: TREATMENT OF NASOLABIAL FOLD WRINKLES

The proposed indication for Isolagen Therapy™ is for the treatment of moderate to severe nasolabial fold wrinkles in adults ≥ 18 years of age. The primary basis for this label claim is the results of two randomized, placebo-controlled, double-blind, Phase III studies (IT-R-005 and IT-R-006) that randomized 210 subjects to Isolagen Therapy™ and 211 subjects to placebo. Criteria for enrollment were that subjects had to have moderate to severe nasolabial fold wrinkles on both sides of the face and to be "dissatisfied" or "very dissatisfied" with the appearance of the lower part of their face. Subjects were to receive three injections of Isolagen Therapy™ or placebo to both nasolabial fold wrinkles. Subjects responses were assessed by both the subject and a blinded Evaluator immediately prior to their last treatment and at 2, 4 and 6 months after their last treatment for improvement in the appearance of their treated wrinkles. The wrinkle assessments performed at 6 months were used for the primary statistical evaluation of clinical efficacy.

The co-primary efficacy endpoints for studies IT-R-005 and IT-R-006 were the following:

> Subject Wrinkle Satisfaction Assessment: the subject live comprehensive assessment of the wrinkles of the lower part of the face at visit 6, using a 5-point wrinkle satisfaction scale, where a response is defined as a two point or better improvement on the scale when compared to baseline
>
> Evaluator Wrinkle Severity Assessment: the blinded evaluator live assessment of the bilateral nasolabial fold wrinkles at rest, at visit 6, using a 6-point ordinal wrinkle severity scale with a photoguide, where a response is defined as a two point or better improvement on the scale compared to baseline

The primary efficacy results from both studies were highly statistically significant, showing a greater proportion of subjects in the Isolagen Therapy™-randomized group compared to the placebo-randomized group who met the stringent, protocol-defined criteria for a positive response to treatment (see section 5.1.2). These criteria included two co-primary endpoints, the first based on an impartial assessment of wrinkle severity by a blinded Evaluator and the second based on an assessment of subject satisfaction with the wrinkles on the lower part of the face. A 2-point improvement for *both* nasolabial fold wrinkles on the Evaluators' 6-point assessment scale or a 2-point improvement on the subjects' 5-point assessment scale was required to meet the protocol-specified criteria for response to treatment. Statistical evaluation of secondary efficacy assessments also showed that a significantly greater proportion of subjects in the Isolagen Therapy™-randomized group compared to the placebo-randomized group achieved at least a 1-point improvement on the evaluator and subject wrinkle assessment scales after only two treatments. A 1-point improvement in wrinkle severity or subject satisfaction represents a clinically meaningful outcome for the patient.

Intradermal administration of Isolagen Therapy™ in the area of nasolabial fold wrinkles and other facial wrinkles is safe, with transient appearance of redness and swelling

around the site of injection the most common adverse effect of treatment. There were no serious adverse events considered related to Isolagen Therapy™ treatment over the course of Isolagen's clinical development program for this indication. The integrated safety results from seven clinical trials of Isolagen Therapy™ for the treatment of facial rhytids are presented in Section 6 of this briefing document.

1.4. MARKET CONTEXT: COMPARISON OF ISOLAGEN THERAPY™ TO CURRENTLY AVAILABLE TREATMENTS FOR NASOLABIAL FOLD WRINKLES

Aesthetic plastic surgeons, dermatologists and other cosmetic physicians are frequently contacted by patients seeking rejuvenation of the appearance of aging skin. The American Society for Aesthetic Plastic Surgery (ASAPS) reported that from 1997 to 2007, cosmetic procedures increased by 497% to over 11.6 million procedures, non-surgical procedures accounting for seven million of these (ASAPS 2007). Nonsurgical options for the treatment of facial lines, wrinkles and folds include neurotoxins, fillers, lasers, non-ablative therapies, microdermabrasion and chemical peels.

The treatment options currently available for nasolabial folds are primarily dermal fillers (Baumann 2004). Hyaluronic acid (bacterially synthesized or isolated from sources such as rooster combs), collagen (of human or bovine origin), or other synthetic substances, are injected into the region of the wrinkle to correct the perceived defect. The degree of correction is achieved through the immediate space-filling effect of the injection, as determined by the eye of the treating physician. While the safety of dermal fillers and their duration of effect has improved with newer generation products, the effect of all such products is temporary, declining as the injected material is gradually degraded by natural processes.

Although, like dermal fillers, Isolagen Therapy™ is intended to improve the appearance of wrinkles associated with aging, Isolagen Therapy™ is quite distinct from dermal fillers in its mechanism of action and the onset and potential duration of its effect. Isolagen Therapy™ is a biological therapy that employs living fibroblasts to induce microstructural changes in the skin. Thus, wrinkle correction induced by Isolagen Therapy™ is not immediate, but occurs over a period of weeks following treatment. Further, the effect of Isolagen Therapy™ may be relatively long-lasting, since wrinkle correction is believed to be achieved through biological renewal and/or remodeling of the microstructure of the skin rather than through an artificial space-filling effect; however, the long-term duration of the effect of Isolagen Therapy™ is not currently known.

If approved, Isolagen Therapy™ will offer a unique alternative to dermal fillers for the treatment of nasolabial fold wrinkles by correcting the perceived defect through a biological mechanism.

2. HISTORY OF DEVELOPMENT OF ISOLAGEN THERAPY™

Section 2.1 below summarizes the data known to Isolagen, obtained from available sources, which describes the previous domestic and international commercial experience

of Isolagen Therapy™. Section 2.2 describes the regulatory history of Isolagen Therapy™ under the U.S. FDA.

2.1. OVERVIEW OF PREVIOUS COMMERCIAL EXPERIENCE

The use of autologous human fibroblasts for treatment of contour deformities was pioneered in 1992 by Dr. William K. Boss and his work in the area of dermal repair. He removed a small piece of skin from a patient's wrist and cultured the autologous fibroblasts from the biopsy. The autologous cells were injected into a crease in the skin of the patient's wrist and the crease was observed to decrease over time. He observed the area serially for several years and noted that the crease at the injection site remained diminished. There were no adverse reactions to this single treatment (personal communication, Dr. William Boss, 1999).

From December 1995 to February 1999, Isolagen Therapy™ was marketed in the United States as a cosmetic treatment to correct facial defects, such as wrinkles, depressions and scars, as well as lip augmentation. Literature reports also state that Isolagen Therapy™ was utilized with success as an adjunct to chemical peels, laser resurfacing (either before or after the laser treatment), and botulinum toxin injections, as a treatment for stretch marks and to prolong the results of bovine collagen injection (Boss and Marko 1998, Boss et al. 2000a). Material for the U.S. commercial experience was manufactured at Isolagen's New Jersey facility (which has since been closed) using a predecessor manufacturing process. The U.S. commercial experience included about 200 clinicians in the fields of dermatology, facial plastic surgery, and reconstructive plastic surgery. There was a reported patient experience of approximately 1,200 patients with approximately 4,700 injections performed. A subjective patient satisfaction survey showed 92% of the patients were satisfied with the grade of correction after 12 months and 70% after 36-48 months (Boss et al. 2000b). Of the total treated individuals, 354 patients who had received at least a test dose of Isolagen Therapy™ were included in a retrospective analysis to assess safety during commercialization. Fifty-four people (15%) had reported at least one adverse event, with the most common related adverse events being injection site inflammation (14 patients) and injection site edema (13 patients). Almost all of the related adverse events were considered to be of mild or moderate severity. Isolagen discontinued marketing of Isolagen Therapy™ in the U.S. in February 1999 when the FDA required all somatic cell therapies to file Investigational New Drug applications (IND) and follow a formal approval process. Isolagen initiated U.S. clinical trials of Isolagen Therapy™ under IND in 2003.

In addition to the previous U.S. commercialization, Isolagen Therapy™ was sold with limited distribution in the United Kingdom (UK) from 2002 to 2007 and in Australia from 2003 to 2004. Autologous cell material was manufactured at Isolagen's United Kingdom (UK) facility located in London, England or at Isolagen's Sydney, Australia facility based on the marketing region. Over 6,000 patients were treated with Isolagen Therapy™ in the UK; there are no data regarding patient treatment in Australia. The Australian facility closed all operations in early 2005 and the UK facility closed all operations in early 2007 as a result of business decisions. The number of adverse events reported to Isolagen from the international experience has been small, with an estimated

report rate of ≤ 0.4% per patient in the UK. The adverse events reported appear to be similar to the US experience in number, severity and type.

2.2. U.S. REGULATORY HISTORY

As described above, Isolagen Therapy™ was marketed in the U.S. as a cosmetic treatment from December 1995 to February 1999 until the FDA required federal regulation of somatic cellular therapies. Isolagen's original IND for the treatment of facial contour deformities was accepted for Agency review in May 2002. At the time of filing, the clinical indications covered by the IND included treatment of rhytids, dermal depressions, and acne scars. However, the clinical indication for the IND was narrowed at the request of the FDA to the treatment of facial rhytids (wrinkles) in January 2003.

The clinical studies performed under IND were conducted in accordance with standard research approaches and were designed utilizing key regulatory guidance and advice from the FDA. Following early studies to obtain initial safety data and to confirm the dose and dose regimen for Isolagen Therapy™ administration, Isolagen conducted two Phase III efficacy studies that were intended to provide pivotal evidence of the efficacy and safety of Isolagen Therapy™ in the treatment of nasolabial folds and glabellar lines. These Phase III studies (IT-R-003A and IT-R-003B) were conducted in accordance with a Special Protocol Assessment (SPA) agreement with the FDA, and included two co-primary endpoints based on independent wrinkle assessments performed by a blinded Evaluator and by the subject. In both studies, a higher response rate was observed in the Isolagen Therapy™-randomized population compared to the placebo-randomized population for both co-primary endpoints. However, in study IT-R-003A, the endpoint based on the Evaluator's assessment failed to meet the criteria for statistical significance. Upon evaluation of these and other data, Isolagen determined that inconsistency in Investigator training in injection technique and wrinkle assessment may have contributed, in part, to the failure of the IT-R-003A study to meet the prospective criteria for demonstration of efficacy. Isolagen designed a new Phase III protocol in consultation with the FDA that incorporated several modifications to the previous study design. The revised Phase III protocol was approved under a SPA by the FDA and two identical pivotal studies, IT-R-005 and IT-R-006, were conducted for the treatment of nasolabial folds. By August 2008 the primary efficacy and safety data for both pivotal studies had been analyzed, and the blinded Evaluator and subject assessments met the co-primary endpoints with a high level of statistical significance (p-values ranging from <0.0001 to 0.0075). Isolagen filed an original BLA with the FDA in March 2009 which was accepted for review in May 2009.

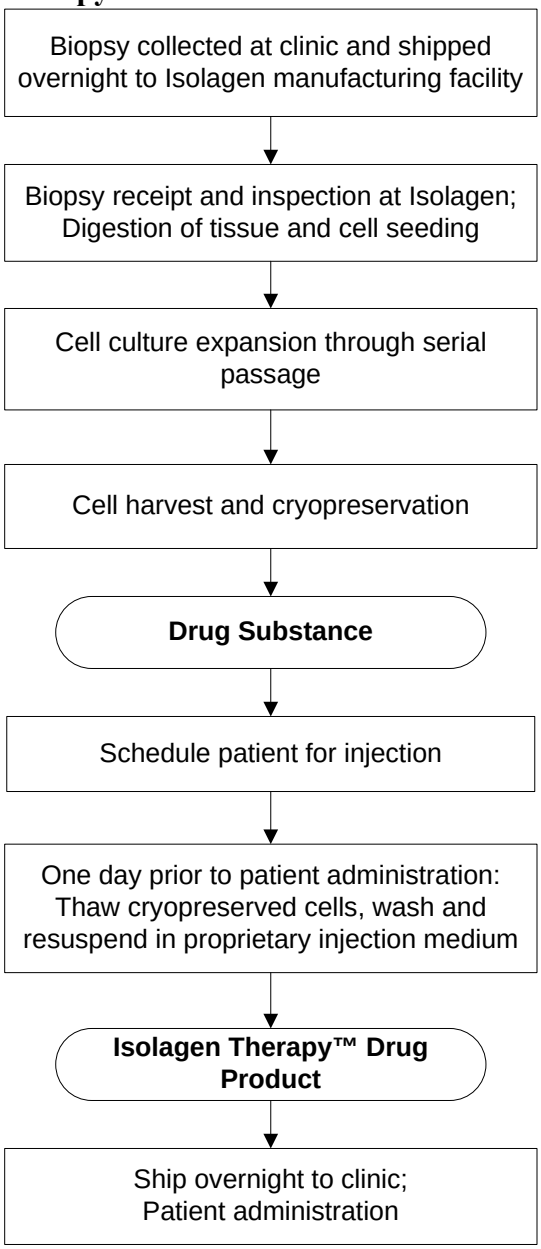
3. PRODUCT MANUFACTURE AND TESTING

3.1. MANUFACTURING PROCESS

The proposed commercial Isolagen Therapy™ manufacturing process is initiated by collection of a skin biopsy (epidermal and dermal layers) from the post-auricular area of the patient seeking treatment. The quantity of tissue collected, three 3-mm circular

biopsies, provides a sufficient number of cells for seeding in culture, while minimizing the pain and disruption for patients. The biopsy is shipped overnight in a controlled temperature (2-8ºC) shipping container (provided by Isolagen) to Isolagen's commercial manufacturing facility in Exton, PA. Upon receipt at Isolagen, the biopsy is examined to ensure it meets Quality Control criteria for further processing. If found acceptable, the tissue is washed in sterile medium containing antibiotics, and treated with a cocktail of digestive enzymes that release the cells from the biopsied tissue. The isolated cells are seeded into a tissue culture vessel and propagated and expanded by serial passage using cell culture techniques to obtain a quantity of cells sufficient for three consecutive treatments of the patient's treatment area. Antibiotics are not used in the culture medium after the first cell feeding. When a sufficient number of cells have been obtained, the bulk cell suspension is cryopreserved until the patient can be scheduled at the physician's office for their initial and subsequent treatments with Isolagen Therapy™. One day prior to each scheduled visit, an aliquot of cryopreserved cells is thawed and washed in sterile medium. The cells are resuspended to a concentration of $1.0 – 2.0 \times 10^7$ cells/mL in proprietary injection medium. Two vials of Isolagen Therapy™ Drug Product, each containing 1.2 mL cell suspension, are prepared for each treatment administration. This is a quantity sufficient to treat two nasolabial fold wrinkles with a total combined length of ≤ 20 cm, where Isolagen Therapy™ is injected in a volume of 0.1 mL/linear centimeter. The vials of Isolagen Therapy™ Drug Product are shipped immediately upon manufacture to the clinical site using a controlled temperature (2-8ºC) shipping container and an overnight delivery service. The Drug Product is stable at 2-8°C for up to 48 hours prior to injection. Figure 1 provides a schematic flow diagram of the Isolagen Therapy™ manufacturing process from biopsy collection to Isolagen Therapy™ delivery to the clinical site.

Figure 1. Schematic Flow Diagram of Manufacturing Process for Isolagen Therapy™



3.2. PRODUCT CHARACTERIZATION AND RELEASE

The Isolagen Therapy™ Bulk Drug Substance and final Drug Product must meet certain Quality Control criteria prior to being released for further product manufacture or for patient administration, respectively (Table 1). Each lot of Bulk Drug Substance is confirmed to pass tests for sterility, mycoplasma contamination and endotoxin content. In addition, the Bulk Drug Substance is tested to verify the concentration, viability and purity of the cell suspension. Purity is evaluated based on the percentage of cells that stain positively with a fibroblast-specific cell surface marker. Typically, close to 100%

of cells in the Bulk Drug Substance are found to express fibroblast-specific cell surface antigens.

The Isolagen Therapy™ Drug Product is prepared on the day immediately prior to patient administration and must be used within 48 hours of its release. The entire manufacturing process is conducted using aseptic processing techniques and microbiological controls for assurance of sterility of the Drug Product, and takes approximately three months using the commercial process. Sterility testing on the Drug Product is conducted by both standard sterility tests (requiring a 14 day incubation period) and a Gram stain. Since the product must be injected prior to the availability of the 14 day incubation period, the product is released based on negative results from the Gram stain test. In the event of a sterility test failure after the product has been administered, the clinical site will be notified and appropriate patient follow-up initiated. There have been no positive Gram stain tests or sterility test failures during the release testing of Isolagen Therapy™ at Isolagen's manufacturing facility in Exton, PA.

Table 1 summarizes the release tests performed on the Isolagen Therapy™ Bulk Drug Substance and Drug Product.

Table 1. Testing of Isolagen Therapy™ Bulk Drug Substance and Drug Product for Product Release

Commodity	Test
Isolagen Therapy™ Bulk Drug Substance	Sterility
	Mycoplasma
	Endotoxin
	Cell Count
	Cell Viability
	Purity/Identity
Isolagen Therapy™ Drug Product	Sterility
	Gram Stain
	Cell Count
	Cell Viability
	Collagen Content

3.3. PLANS FOR COMMERCIAL DISTRIBUTION OF ISOLAGEN THERAPY™

Isolagen Therapy™ is a living biological material, requiring controlled conditions of storage and handling from the collection of the original biopsy material to the time of patient administration. The final product has a relatively short shelf life (48 hours), requiring careful coordination between the manufacturing and clinical sites to ensure that

the patient is available to receive their injection on the day after the product is manufactured. Also, sample tracking and accountability procedures are essential for assurance that the cells received by each patient are derived from the same patient's biopsied tissue. This section provides an overview of the planned logistics for commercial Isolagen Therapy™ manufacture and distribution.

3.3.1. Patient Selection

Patients appropriate for treatment with Isolagen Therapy™ should be ≥ 18 years of age with moderate to severe nasolabial fold wrinkles. The skin behind the ear (the origin of the dermal fibroblasts to be cultured) should be healthy in appearance, without indications of sunburn or scarring. Patients will be counseled regarding the gradual, rather than immediate, improvement in the appearance of the treated wrinkles.

3.3.2. Clinician Training and Certification

Isolagen will provide Isolagen Therapy™ only to trained practitioners who are specially certified in the Isolagen Therapy™ Program. Only certified prescribers will be able to administer Isolagen Therapy™. The Isolagen Therapy™ Program will include biopsy and Isolagen Therapy™ injection training, as described below. In addition, physicians must attest in writing to their willingness to follow the appropriate procedures for Isolagen Therapy™ administration, provide appropriate counseling and safety surveillance for patients, and report promptly to Isolagen any adverse events associated with Isolagen Therapy™ administration.

Isolagen plans to establish Centers of Excellence, to facilitate the proper training of physician prescribers. These centers will employ Isolagen-trained staff who specialize in facial aesthetic treatments. Training of physician prescribers at the Centers or at their own clinical site will include the following:

- Proper biopsy collection and shipment to Isolagen
- Proper treatment preparation and injection technique for Isolagen Therapy™ administration
- Proper logistics training from biopsy to injection tracking to ensure administration of the patient-specific cells to only the indicated patient.
- Types and severity of AEs expected with intradermal Isolagen Therapy™ administration and appropriate medical treatment, follow-up and reporting.

3.3.3. Scheduling of Isolagen Therapy™ Manufacture and Patient Administration

The treating physician will schedule a biopsy in coordination with the Isolagen manufacturing facility to ensure that there is sufficient manufacturing capacity to process the biopsy prior to its collection. Physicians may schedule more than one biopsy on a single day.

Isolagen will supply the treating physician with a biopsy punch, vials containing sterile buffered saline for biopsy collection, biopsy vial labels to record patient-specific information, a biopsy inventory form to record all biopsies included in a single shipment,

and an insulated shipping container with freezer blocks, shipping labels and other materials necessary to ensure the integrity and control the temperature of the biopsy during shipment. The physician must supply all other materials necessary for anesthetizing and sterilizing the skin area to be biopsied, tools for collection of the biopsy (other than the biopsy punch), and materials for dressing the biopsy collection site as needed. If more than one patient will be biopsied at the clinical site on the same day, all labeling and packing of each biopsy must be completed before proceeding to the next patient. Biopsies may be scheduled and shipped on Monday through Thursday only, to ensure that they will be received by Isolagen and processing of the tissue can begin during the standard work week.

Upon receipt of a biopsy at the Isolagen manufacturing facility, the shipping container, documentation and biopsied tissue are all examined by Isolagen Quality Control representatives to ensure that the tissue is adequate for initiation of Isolagen Therapy™ manufacture and that all patient-specific information has been correctly recorded. In the event that the biopsy is found unacceptable, re-biopsy of the patient is possible, using tissue from behind the other ear.

Once the patient-specific fibroblasts have been expanded sufficiently in culture and the cryopreserved Bulk Drug Substance has been determined to meet the criteria for manufacture of Isolagen Therapy™ Drug Product, the clinical site is contacted so that the patient can be scheduled for three Isolagen Therapy™ doses, administered at an interval of 5 weeks ± 1 weeks. One dose (two vials containing 1.2 mL cell suspension) of Isolagen Therapy™ Drug Product is manufactured according to the procedure described in Section 3.1 on the day prior to each patient administration and is shipped for overnight delivery to the clinical site. Optimally, Isolagen Therapy™ should be administered on the day of receipt by the clinic, but will remain stable at 2-8ºC for up to 48 hours from the time of product release.

3.3.4. Control of Patient-Specific Tissue and Drug Product

Isolagen Therapy™ is an autologous therapy. Thus, it is essential that the system for biopsy acquisition, Isolagen Therapy™ manufacture and patient administration ensures that the cells received by each patient are derived from the same patient's biopsied tissue. The following paragraphs describe the system established by Isolagen to track patient-specific tissue and cells throughout the Isolagen Therapy™ manufacturing process and return to the patient.

At the clinical site, a patient's skin biopsy is collected into a vial containing sterile buffered saline and labeled with the patient's initials and date of birth. The biopsy is shipped accompanied by a biopsy inventory form that specifies the clinical site of origin, the date of biopsy collection, and patient-specific information for each biopsy.

At the Isolagen manufacturing facility, biopsies that are accepted for Isolagen Therapy™ manufacture are given a unique part number and lot number, and all processes and procedures for that patient's material are tracked via these numbers. The initial batch record for each lot is labeled with the patient-specific information to provide a link

between the patient-specific tissue and the manufacturing lot number. All manufacturing documents, cell culture vessels, and in-use equipment are labeled with relevant part numbers and lot numbers. The cryopreserved drug substance and the final product for injection are labeled with the patient-specific information, part number and lot number. Finally, the treating physician and patient will verify the patient initials and date of birth against the information on the vial label as a final check prior to Isolagen Therapy™ administration.

4. CLINICAL DEVELOPMENT PROGRAM

4.1. OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

Isolagen Therapy™ has been tested for the treatment of facial wrinkles and creases in two Phase II studies (Studies IT-R-001 and IT-R-007) and five Phase III studies (Studies IT-R-002, IT-R-003A, IT-R-003B, IT-R-005, and IT-R-006). These trials are considered directly supportive of the clinical development of Isolagen Therapy™ for the treatment of nasolabial fold wrinkles. Studies IT-R-003A, IT-R-003B, IT-R-005 and IT-R-006 provide robust, well-controlled data demonstrating the safety and efficacy profile of Isolagen Therapy™. The earlier IT-R-001 and IT-R-002 trials provided supportive, exploratory data that guided the design of the IT-R-003A/B and IT-R-005/006 trials. Study IT-R-007 provides additional data in support of the safety of Isolagen Therapy™ administration to the face. An overview of the studies conducted as part of the clinical development of Isolagen Therapy™ for the treatment of nasolabial fold wrinkles is presented in Table 2.

Table 2. Overview of Clinical Trials Supporting the Use of Isolagen Therapy™ for Treatment of Nasolabial Folds

Study Number & Phase	Design & Control Type	Dose & Regimen	Diagnosis Inclusion Criteria	Number of Subjects Treated	Timing of Efficacy and Safety Evaluation	Outcome Measures	Study Results
IT-R-001 Phase I/II	Randomized, double-blind, parallel groups; Placebo-controlled	0.5, 1.0, & 2.0 x 10^7 cells/mL Up to 1.0 mLi 0.1 mL/linear cm Intradermal Every two weeks for three treatments	Rhytids for which cosmetic treatment is appropriate	0.5 x 10^7: 10 1.0 x 10^7: 10 2.0 x 10^7: 10 Placebo: 10 N=40	3 months following third study treatment Long Term Safety: 12 month follow- up	Investigator Assessment on 5-point scale three months after third treatment	Isolagen Therapy™ safety comparable to placebo; 2.0 x 10^7 cells/mL was associated with the greatest subject-reported efficacy
IT-R-002 Phase III	Randomized, double-blind, parallel-groups; Placebo-controlled	2.0 x 10^7 cells/mL Up to 2.0 mL Intradermal Every two weeks for three treatments	Facial rhytids or facial scars for which cosmetic treatment is appropriate	N= 151 Isolagen Therapy™: 112 Placebo: 39	4 months following first study treatment Long Term Safety: 12 month follow- up	Investigator Assessment on 7-point scale three months after first treatment	Statistically significant improvement in investigator's evaluation of facial deformities compared to placebo; Isolagen Therapy™ safety comparable to placebo
IT-R-003A Phase III	Randomized, double-blind, parallel-groups; Placebo-controlled	2.0 x 10^7 cells/mL 0.1 mL/linear cm Up to 1.0 mL Intradermal Every seven to fourteen days for three treatments	One nasolabial fold deformity and one glabellar deformity with severity of two or greater	N=107 Isolagen Therapy™: 48 Placebo: 59	6 months following first study treatment Long Term Safety: 12 month follow-up	Blinded Assessor Assessment on 6-point ordinal scale* & Subject VAS six months after first treatment	Subject rating of deformity was significantly improved in the Isolagen Therapy™ group compared to placebo; Isolagen Therapy™ safety comparable to placebo
IT-R-003B Phase III	Randomized, double-blind, parallel groups; Placebo-controlled	2.0 x 10^7 cells/mL 0.1 mL/linear cm Up to 1.0 mL Intradermal Every seven to fourteen days for three treatments	One nasolabial fold deformity and one glabellar deformity with severity of two or greater	N=106 Isolagen Therapy™: 52 Placebo: 54	6 months following first study treatment Long Term Safety: 12 month follow-up	Blinded Assessor Assessment on 6-point ordinal scale* & Subject VAS six months after first treatment	Subject and investigator ratings of the deformity were significantly improved in the Isolagen Therapy™ group compared to placebo; Isolagen Therapy™ safety comparable to placebo

Study Number & Phase	Design & Control Type	Dose & Regimen	Diagnosis Inclusion Criteria	Number of Subjects Treated	Timing of Efficacy and Safety Evaluation	Outcome Measures	Study Results
IT-R-005 Phase III **Pivotal SPA**	Randomized, double-blind, parallel groups; Placebo-controlled	1.0-2.0 x 10^7 cells/mL 0.1 mL/linear cm Up to 2.0 mL Intradermal Every five weeks for three treatments	Evaluator severity of at least three; subject Dissatisfied or Very Dissatisfied with nasolabial fold wrinkle appearance	N=175 Isolagen Therapy™: 83 Placebo: 92	6 months following third study treatment Long Term Safety: 12 month follow-up	Evaluator Wrinkle Severity Assessment on 6-point scale* & Subject Wrinkle Assessment on 5-point scale	Subject and investigator ratings of the deformity were significantly improved in the Isolagen Therapy™ group compared to placebo; Isolagen Therapy™ safety comparable to placebo
IT-R-006 Phase III **Pivotal SPA**	Randomized, double-blind, parallel groups; Placebo-controlled	1.0-2.0 x 10^7 cells/mL 0.1 mL/linear cm Up to 2.0 mL Intradermal Every five weeks for three treatments	Evaluator severity of at least three; subject Dissatisfied or Very Dissatisfied with nasolabial fold wrinkle appearance	N=197 Isolagen Therapy™:98 Placebo:99	6 months following third study treatment Long Term Safety: 12 month follow-up	Evaluator Wrinkle Severity Assessment on 6-point scale & Subject Wrinkle Assessment on 5-point scale	Subject and investigator ratings of the deformity were significantly improved in the Isolagen Therapy™ group compared to placebo; Isolagen Therapy™ safety comparable to placebo
IT-R-007 Phase II	Multicenter, open-label; Uncontrolled "Full Face"	1.0-2.0 x 10^7 cells/mL Up to 6 mL 0.05 mL/linear cm Intradermal Every five weeks for two treatments	Glogau Wrinkle Assessment of 2 or 3; Dissatisfied or Very Dissatisfied with wrinkle appearance	N=45	6 months following first study treatment Long Term Safety: 12 month follow- up	Subject Wrinkle Satisfaction Assessment & Independent Panel Global Review six months after second treatment	Safety of 6 mL dose established

4.1.1. Study IT-R-001 (Phase II)

Study IT-R-001 was a Phase II double-blind, randomized, and placebo-controlled study of Isolagen Therapy™ for the treatment of rhytids, including nasolabial and melolabial folds, perioral lines, glabellar lines, acne scars, and forehead. Forty-one subjects who met the entrance criteria were enrolled and randomized to treatment with one of three dose levels of Isolagen Therapy™ (0.5×10^7 cells/mL, 1.0×10^7 cells/mL, and 2.0×10^7 cells/mL) or placebo. In the acute phase of the study, subjects received three treatments of Isolagen Therapy™ (at one of three dose levels) or placebo administered approximately every two weeks and were followed for safety and efficacy for four months after the first injection. After completion of the acute phase of the study, subjects that received treatment with placebo or the lowest dose level of Isolagen Therapy™ were given the opportunity to receive treatment at the highest dose level of Isolagen Therapy™. All subjects were followed for 12 months after their initial treatment. The endpoints included an Investigator assessment of the primary treatment area four months after the first injection using a 5-point ordinal scale with photoguide, the subject's assessment of the treatment area based on a Visual Analog Scale (VAS), incidence of AEs, and change from Baseline in laboratory evaluations. Forty subjects were treated with Isolagen Therapy™ (N=30) or placebo (N=10) in the acute phase of the study.

Study IT-R-001 was not powered to show statistically significant differences between treatment groups, or between treatment groups and Baseline, and no statistically significant differences were observed, except for the difference in the subject assessment at 4 months relative to baseline for the group receiving the highest dose level of Isolagen Therapy™ (2.0×10^7 cells/mL). Although of limited statistical significance, these data suggested a trend toward greater efficacy with higher cell numbers. Administration of Isolagen Therapy™ to facial rhytids appeared to be safe, with possibly related adverse events being limited to injection site effects of mild or moderate intensity.

4.1.2. Study IT-R-002 (Phase III)

Study IT-R-002 was a Phase III double-blind, randomized and placebo-controlled study of Isolagen Therapy™ for the treatment of facial contour deformities and scars, including the glabellar area, nasolabial folds, melolabial folds, periorbital lines, perioral lines (vermillion border), forehead lines, acne vulgaris scars, and pock marks. In the acute phase of this study, each subject was to receive three treatments of Isolagen Therapy™ containing 2.0×10^7 cells/mL or placebo, administered every 14 ± 7 days. One hundred fifty-one (151) subjects were treated with Isolagen Therapy™ (N=112) or placebo (N=39) in the acute phase of the study. The primary efficacy endpoint was the Investigator's assessment of wrinkle severity 4 months after the first treatment, using a 7-point ordinal scale with a photoguide. Several secondary endpoints were included in the study to evaluate alternative approaches to efficacy assessment by the Investigator, the subject or an independent reviewer, and to assess the efficacy of Isolagen Therapy™ compared to placebo at 6 months after the first treatment. Isolagen Therapy™ treatment

was found to result in a greater proportion of responders than placebo treatment by a statistically significant margin for the primary efficacy endpoint as well as for several of the secondary endpoints evaluated at 4 months. At 6 months, all efficacy endpoints demonstrated statistically significant results. These data provided early clinical evidence of the effectiveness of Isolagen Therapy™ for treatment of facial rhytids.

With respect to safety, most adverse events were reported in approximately equal proportion between Isolagen Therapy™- and placebo-treated subjects with the exception of injection-site edema, which was more common in Isolagen Therapy™-treated subjects. There was one adverse event of edema considered severe in the Isolagen Therapy™-treated population. All injection site edema events resolved.

4.1.3. Studies IT-R-003A and IT-R-003B (Phase III)

Study IT-R-003A and Study IT-R-003B were Phase III double-blind, randomized and placebo-controlled studies of Isolagen Therapy™ for the treatment of contour deformities, specifically nasolabial fold wrinkles and glabellar lines. These studies were conducted concurrently under identical protocols that were developed with the FDA under a Special Protocol Assessment (SPA). The studies were designed to provide pivotal clinical evidence of the effectiveness of Isolagen Therapy™ for the treatment of facial contour deformities. In the acute phase of these studies, each subject was to receive three treatments of Isolagen Therapy™ containing approximately 2.0×10^7 cells/mL or placebo, administered every seven to 14 days. The co-primary endpoints of each study were the proportion of responders based on the blinded Evaluator's assessment of the severity of the primary nasolabial fold and based on the subject's assessment of wrinkle severity using a Visual Analog Scale (VAS). The Evaluator's assessment scale was the 6-point ordinal wrinkle severity scale for the assessment of nasolabial folds developed and validated by Lemperle et al. (Lemperle, 2001). Success for this endpoint was defined as a 2-point improvement in the severity of the primary nasolabial fold. The subject's VAS scale asked subjects to rate each treated contour deformity from 0 (no defect) to 100 (very severe defect) by placing a mark on a 10 cm line.

Across both studies, 213 subjects were treated with Isolagen Therapy™ (N=100) or placebo (N=113) in the acute phase of the trials. In both the IT-R-003A and -003B studies, statistically significant differences in response between Isolagen Therapy™-treated and placebo-treated subjects were observed for the subject VAS assessment. For the co-primary endpoint based on the Evaluator's assessment of wrinkle severity, there was a statistically significant difference in responders in the Isolagen Therapy™-treated group compared to the placebo-treated group for study IT-R-003B only. In study IT-R-003A, a greater percentage of Isolagen Therapy™-treated subjects were scored as responders by the Evaluator assessment than placebo-treated subjects, but the difference did not meet statistical significance. The key efficacy results from the IT-R-003A/B studies are presented in section 5.4 of this briefing document.

For the evaluator assessment for study IT-R-003A, the differences between the response rate for Isolagen Therapy™ and placebo were not statistically significant. Also, differences in response rates were observed between clinical sites in studies IT-R-003A and IT-R-003B. Differences in wrinkle assessment technique and other factors may account for the observed variability. These observations led Isolagen to re-evaluate the design of the IT-R-003A and IT-R-003B clinical trials and to develop a new protocol for additional pivotal Phase III trials for Isolagen Therapy™. Among the changes introduced into the new protocol design were: (1) an increase in the quantity of Isolagen Therapy™ available for each treatment, to ensure adequate product to treat the entire area to be evaluated; (2) a limitation on the number of Injectors and Evaluators at each clinical site to no more than two of each, and training of each Investigator; (3) increasing the time between treatments to provide more time for resolution of any residual inflammation from the previous injection; (4) modifying the minimum enrollment criterion for wrinkle severity from grade 2 to grade 3; and (5) use of a 5 point subject self assessment scale evaluating satisfaction with the appearance of wrinkles in the lower part of the face (Cohen and Holmes, 2004). The change to only enroll subjects with nasolabial fold wrinkle severity of grade 3 or higher was introduced to address potential bias of Evaluators against appropriately scoring the response of treated subjects who might have entered the study with a wrinkle severity score of grade 2 and who achieved a 2-point improvement to grade 0 (no wrinkle visible).

Two new identical Phase III pivotal studies (IT-R-005 and IT-R-006) were conducted based on the improved protocol design and based on discussion with FDA under SPA, as described in Section 4.1.4.

4.1.4. Pivotal Studies IT-R-005 and IT-R-006

Pivotal studies IT-R-005 and IT-R-006 were Phase III multicenter, double-blind, randomized, placebo-controlled studies of the efficacy and safety of Isolagen Therapy™ in the treatment of nasolabial fold wrinkles. The studies were conducted concurrently at 13 sites according to an identical protocol. The adequacy of the protocol design to form the primary basis of an efficacy claim was agreed to by the FDA under a Special Protocol Assessment. The rationale underlying the design of these pivotal clinical trials is described in Section 4.2, below. The results of the studies are described in detail in Section 5.1.

4.1.5. Study IT-R-007

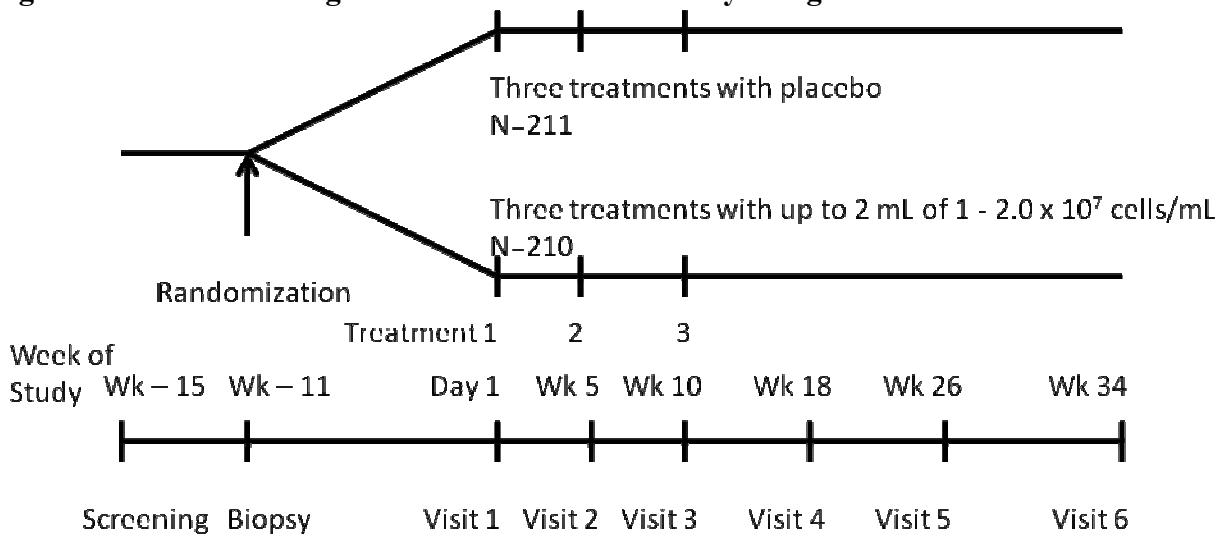
Study IT-R-007 was a Phase II multicenter, open-label study of the safety and efficacy of Isolagen Therapy™ in the treatment of multiple facial wrinkles and creases, other than nasolabial folds. In the acute phase of this study, each subject (45 in total) received two treatments of up to 6 mL of Isolagen Therapy™ containing 1.0-2.0 x 10^7 cells/mL, administered every five weeks ± 10 days. This study exposed subjects to a three-fold

higher total dose of Isolagen Therapy™ than was used in the pivotal IT-R-005/006 studies. The safety data from Study IT-R-007 have been included in an integrated analysis of the safety of Isolagen Therapy™, discussed in Section 6 of this document.

4.2. PIVOTAL STUDY DESIGN

The adequate and well-controlled studies demonstrating effectiveness in support of the proposed label claim are the Phase III, multicenter studies IT-R-005 and IT-R-006. These were prospective, multicenter, randomized (1:1 by site), placebo-controlled, double-blind studies. Following a screening visit to evaluate eligibility, eligible subjects returned for three small (3 mm) biopsies of skin taken from behind the ear. At Isolagen, cells were isolated from the biopsy and expanded in culture to create autologous fibroblast suspensions (Isolagen Therapy™) for each subject randomized to Isolagen Therapy™ treatment. To assure the maximum viability of the fibroblasts, the subject's treatments were scheduled to take place on the day the Isolagen Therapy™ (or placebo) was received by the clinical site from Isolagen. Subjects received either Isolagen Therapy™ or placebo in three treatments at five ± one week intervals. The co-primary efficacy endpoints were based on the blinded Investigator's assessment of nasolabial fold wrinkle severity and the subject's blinded assessment of their satisfaction with the wrinkles on the lower part of the face. Both assessments were conducted at six months following the third treatment visit. In addition, long-term safety was assessed via a telephone interview of subjects 12 months following the receipt of the initial treatment; results of the long-term phase of the pivotal studies are summarized in Section 6.2. Figure 2 provides a schematic representation of the design of pivotal studies, IT-R-005 and IT-R-006.

Figure 2. Schematic Diagram of Pivotal Clinical Study Design



4.2.1. Study Populations

In the first clinical study, IT-R-001, Isolagen Therapy™ was evaluated for the treatment of facial rhytids. Subjects ranging from 18 to 70 years of age who requested cosmetic treatment for facial rhytids (including nasolabial and melolabial folds, glabellar lines, periorbital lines, perioral lines, and forehead wrinkles) and met a limited number of exclusion criteria were enrolled.

For the Phase III studies, IT-R-003A and IT-R-003B, the treatment area was more strictly defined to include only subjects with at least one nasolabial fold wrinkle and at least one glabellar line that met a minimum severity of "Moderate Defect" (Grade 2 or higher on a 6-point ordinal scale) as assessed by the Investigator.

The injection treatment area was further refined to include only bilateral nasolabial fold wrinkles for the pivotal Phase III studies, IT-R-005 and IT-R-006, with more stringent eligibility criteria applied. In addition to having to meet a minimum severity of "Moderately Deep Defect" (Grade 3 or higher on a 6-point ordinal scale) for both nasolabial fold wrinkles, as assessed by the Investigator, subjects were also required to be "dissatisfied" or "very dissatisfied" with the wrinkles of their lower face based on a 5-point ordinal, self-assessment scale. Severity of the defect was limited by exclusion of subjects with excessive dermatochalasis of the nasolabial fold area (such that the cheek overlays the wrinkle, preventing the assessment or treatment of the wrinkle), and by exclusion of subjects where the nasolabial fold wrinkles could not be lessened by physically spreading the area apart.

The following exclusion criteria were used in the pivotal studies and in all supportive clinical studies for this indication:

- History of active autoimmune disease or organ transplantation;
- Active or chronic skin disease, including but not limited to psoriasis, eczema, blistering skin disease or local infection;
- Active systemic infection; and,
- Requires chronic antibiotic or steroidal therapy.

For the pivotal studies IT-R-005 and IT-R-006, additional exclusion criteria were included for subjects with known genetic disorders affecting fibroblasts or collagen; use of systemic agents that increase bleeding or clotting, or disorders equated with these effects; and excessive exposure to sun without adequate sun protection, or sunburn to the post-auricular area.

The use of prior or concomitant cosmetic treatment to the nasolabial fold areas (e.g., retinoic acid, prescription level glycolic acid or similar treatment, microdermabrasion,

dermal fillers or facial surgery in the lower 2/3 of the face) was limited in each trial to ensure an accurate representation of the efficacy and safety of Isolagen Therapy™.

4.2.2. Dose and Treatment Schedule

The proposed commercial dose regimen for Isolagen Therapy™ for the treatment of nasolabial fold wrinkles is up to 2 mL of autologous cell suspension at a concentration of 1.0-2.0 x 10^7 cells/mL, administered at 0.1 mL per linear centimeter (up to 20 centimeters total treatment area). A full course of treatment corresponds to three doses administered at an interval of five weeks ± one week. The proposed commercial dose regimen corresponds to the regimen employed in the two Phase III clinical studies, IT-R-005 and IT-R-006, which provide the pivotal evidence of the efficacy of Isolagen Therapy™.

4.2.2.1. Dose

The initial cell concentration for Isolagen Therapy™ was based on the number of cells administered by clinicians before the regulation of Isolagen Therapy™ by the FDA. In the US commercial experience from 1995 to 1999, between 1.1 and 5.8 x 10^7 cells/mL were used for injection.

In the first clinical study conducted under IND, Study IT-R-001, subjects received treatment with up to 1.2 mL of Isolagen Therapy™, at a cell concentration of 0.5, 1.0 or 2.0 x 10^7 cells/mL, or placebo. Each of the proposed doses had a safety profile similar to that of placebo. While the study was not powered to detect statistically significant differences in efficacy between treatment groups, a statistically significant improvement in wrinkle severity from baseline to four months after the initial treatment was observed for the highest dose group only (2.0 x 10^7 cells/mL) based on the subject assessment. Although of limited statistical significance, these data suggested a trend toward greater efficacy with higher cell numbers. For subjects who do not achieve the full desired response to their foundation treatment of three doses, Isolagen is considering clinical evaluation of re-treatment with additional cells, rather than increasing the cellular concentration used for initial treatment.

4.2.2.2. Treatment Schedule

The proposed treatment schedule for commercial use of Isolagen Therapy™ is three doses, delivered at an interval of five weeks ± one week. This treatment schedule was used in the pivotal efficacy studies, IT-R-005 and IT-R-006.

Investigators who participated in previous Phase III studies (IT-R-003A and IT-R-003B) indicated that the protocol-specified time between treatments (7 to 14 days) was insufficient to permit the mild inflammation induced by one injection to subside before administration of the next injection. When administering sequential injections at the longer intervals permitted by the protocol (14 days), Investigators reported that the injection sites were more likely to appear closer to normal, “healed” skin, which led to

greater control of both the depth and volume of injection. However, Investigators indicated that even those longer 14-day intervals were not adequate to allow complete recovery of the area from the previous treatment. Additionally, there was a concern that injecting cells into inflamed tissue could have unpredictable effects on the phenotype of the injected cells.

For these reasons, the interval between successive treatments in the pivotal studies IT-R-005 and IT-R-006 was initially four weeks ± one week. The clinical protocol was amended (Protocol Amendment 1, submitted 25 May 2007) such that the interval from the Baseline/Biopsy visit to first injection was 11 to 22 weeks with subsequent injections every five weeks ± one week.

4.2.3. Treatment Area

Phase III studies, IT-R-003A and IT-R-003B, did not allow for treatment of what is sometimes termed the mesolabial fold wrinkle, which is the fold or wrinkle that extends inferiorly from the corner of the mouth towards the chin. The mesolabial fold wrinkle is frequently contiguous with the nasolabial fold wrinkle. The restriction on treating this portion of the nasolabial fold was not reflective of clinical practice, and may have reduced the apparent efficacy of the product. For the pivotal studies, IT-R-005 and IT-R-006, the maximum total treatment area was increased to allow for treatment of the entire nasolabial fold wrinkle (including the mesolabial fold wrinkle). The length of nasolabial fold wrinkles, including the mesolabial fold wrinkle, may be up to 10 cm per side (Horibe, 1989). As one of the co-primary efficacy assessments in the pivotal studies was the subject's assessment of their satisfaction with the appearance of the lower part of the face (as described in Section 4.2.6), it was important to treat the entire nasolabial fold wrinkle in order to provide the most clinically meaningful treatment benefit. The Isolagen Therapy™ concentration ($1.0 – 2.0 \times 10^7$ cells/mL) and treatment distribution (0.1 mL per linear cm) remained constant throughout most of the clinical development program. However, due to the changes described above, the total maximum dose per treatment was increased in Study IT-R-005 and IT-R-006 to 2 mL over a total treatment area of 20 linear cm.

4.2.4. Blinding of Subject and Evaluator

All clinical studies, with the exception of the Phase II Study IT-R-007, were double-blind through the acute phase (primary efficacy). Each of these studies included a carrier-only placebo that was packaged and administered identically to active treatment. For the purposes of manufacturing management, placebo subject sample destruction, quality control and re-biopsy decisions, the Isolagen Quality Assurance (QA) Manager was not blinded. Randomization information was not provided to Isolagen clinical staff or any clinical site staff. No personnel involved in the processing, production, or shipment of the study product had any involvement in the clinical monitoring, data management, analysis, or interpretation of the trial. Sites were informed of a subject's treatment assignment only after completion of study analyses.

4.2.4.1. Biopsies

During the initial phase of the pivotal clinical studies, re-biopsies were permitted. As only biopsies from subjects who were randomized to active treatment were processed and manufactured, Isolagen devised a procedure for selection of placebo subjects to undergo a re-biopsy in order to maintain the study blind. The biopsies collected from placebo-treated subjects were not further processed.

4.2.4.2. Efficacy Assessments

The blinding procedures employed in the pivotal Phase III studies, IT-R-005 and IT-R-006, utilized two Investigators for each subject. One Investigator administered the treatments and a different Investigator served as the Evaluator. Additionally, Investigators were instructed not to discuss efficacy assessments with the subjects or any other study staff; this was meant to ensure that efficacy assessments remained unbiased. To this end, subject efficacy self-assessments were to be self-administered in a room in the absence of study personnel and prior to the conduct of the other clinic visit assessments.

4.2.5. Method of Treatment Administration

Through previous clinical trials and commercial use in the UK, Isolagen has developed an Isolagen Therapy™ injection technique that results in optimal treatment response. The plane of the injection has been found to be critical to the success of the treatment. Physicians participating in the pivotal clinical studies were trained to inject Isolagen Therapy™ into the superficial papillary dermis (below the epidermis) as described below.

Each vial of study product is thawed, and gently inverted several times prior to gently and aseptically drawing the contents into a syringe. Patients are permitted to receive topical or local anesthesia prior to treatment. A trained physician then proceeds to administer the injections using a fine (29-30 gauge) needle. The time required to complete the injections is dependent on the total area to be treated; however, treatment of both nasolabial folds takes approximately 15-30 minutes after application of local anesthetic.

After treatment, patients may gently apply ice to the treated areas for several minutes. Patients are instructed not to wash or apply creams or makeup to the treated areas for 72 hours following injection.

4.2.6. Primary Efficacy Assessments

The pivotal clinical studies employed two co-primary assessment tools for evaluation of subject response to treatment: one based upon the Investigator's evaluation of wrinkle severity and the other based upon the subject's satisfaction with the appearance of the lower part of their face. The assessment by the blinded Investigator (the Evaluator) was intended to provide an impartial evaluation of wrinkle severity for the purpose of comparing the efficacy of Isolagen Therapy™ to placebo in the setting of a controlled trial. The subject self-assessment was designed to provide a more clinically relevant

measure of the effect of a cosmetic therapy, specifically, based on the subject's assessment of their satisfaction with their appearance. The scales used for each assessment are described below.

It should be noted that the assessments made by the Evaluator were determined independently at each assessment visit, without reference to the wrinkle severity grades assigned at Baseline or at any previous clinic visit. Similarly, the subject's assessments were made "live" at each clinic visit without reference to photographs or other visual information related to the appearance of their face prior to treatment. The use of live assessments was intended to reduce potential bias in the outcomes and capture the Evaluator's or subject's best assessment of the subject's wrinkles on that day; however, given the gradual onset of Isolagen Therapy™ effect, subjects and Evaluators may not perceive the full effect of the treatment at later time points without reference to the subject's Baseline status. Secondary assessments based on comparisons to photographs taken at baseline resulted in a higher percentage of responders for both the Evaluator and subject assessments (see Section 4.2.7 and Section 5.2.3).

4.2.6.1. Investigator Assessment Scale

In the pivotal clinical trials, IT-R-005 and IT-R-006, the Injector and the Evaluator for each study subject were separate individuals to ensure that the evaluations of treatment effect were unbiased by prior knowledge of the treatment (Isolagen Therapy™ or placebo) that had been administered to the subject. The Evaluator Wrinkle Severity Assessment was conducted at the Screening Visit, the Baseline/Biopsy Visit, on the day of (and prior to) the third treatment (Visit 3), and at 2, 4 and 6 months after the third treatment (Visits 4 through 6), where the Visit 6 assessment (6 months after the third treatment) provided the co-primary measure of efficacy.

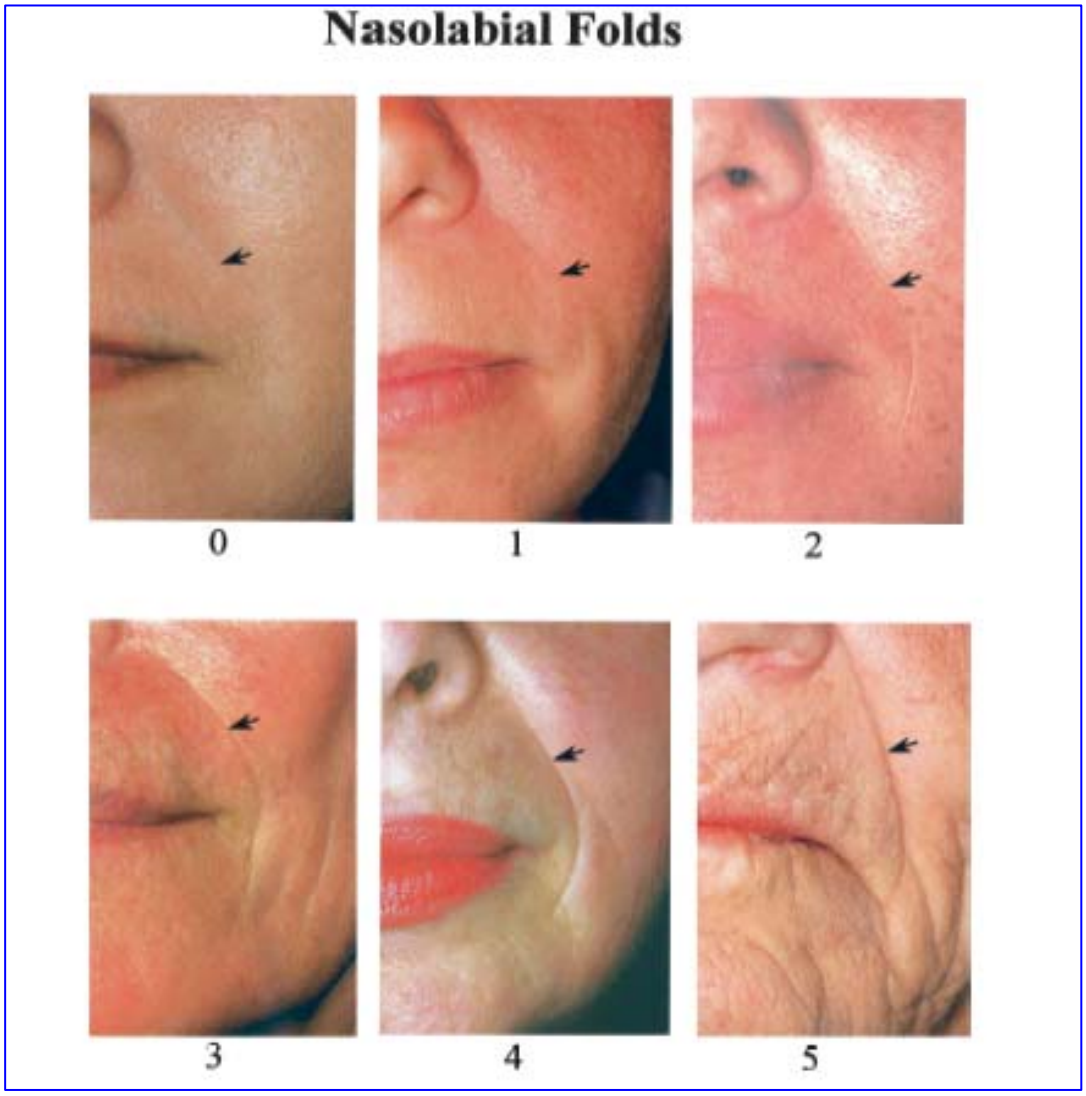
The blinded Evaluator assessed the severity of each nasolabial fold wrinkle separately, using a 6-point ordinal wrinkle severity scale with a photoguide. The assessment of bilateral nasolabial fold wrinkles was based on a published, validated facial wrinkle severity scale (Lemperle, 2001). The grading categories for wrinkle severity are shown in Table 3 the photoguide is shown in Figure 3.

The use of a static wrinkle severity assessment based on the Lemperle Facial Wrinkle Assessment is an accepted standard of measurement in the field of dermatology, and has been employed successfully in pivotal clinical trials for FDA-approved products in similar indications. The addition of descriptive language along with the photoguide served to provide greater consistency of use within and among blinded Evaluators.

Table 3. Evaluator Wrinkle Assessment Scale

Severity Grade	Description of Wrinkle
Grade 0	No wrinkle visible
Grade 1	Just perceptible wrinkle
Grade 2	Shallow wrinkle
Grade 3	Moderately deep wrinkle (definite and distinct wrinkle)
Grade 4	Deep wrinkle, well-defined edge (prominent wrinkle, well-defined edge)
Grade 5	Very deep wrinkle, redundant fold (very severe wrinkle, pronounced edge)

Figure 3. Evaluator Wrinkle Assessment Photoguide



4.2.6.2. Subject Self-Assessment Scale

The Subject Wrinkle Assessment is a comprehensive assessment by the subject of their satisfaction with the appearance of the wrinkles in the lower part of the face, using a 5-point wrinkle assessment scale (Cohen and Holmes, 2004). The subject was instructed to evaluate the current appearance of the wrinkles of the lower part of the face, first smiling and then at rest. Subjects were then required to respond to the question, "How do you feel about the wrinkles in the lower part of your face today?" by selecting one of the responses on the 5-point scale shown in Table 4. Subject assessments were completed

with no study personnel present and prior to the Evaluator's assessments at each visit. Subjects' self-assessments were performed at the Screening Visit, the Baseline/Biopsy Visit, on the day of (and prior to) the third treatment (Visit 3), and at 2, 4 and 6 months after the third treatment (Visits 4 through 6), where the Visit 6 assessment provided the co-primary measure of efficacy.

Table 4. Subject Self-Assessment Scale

Self-Assessment Score	Description of Self-Assessment
-2	I am very dissatisfied with the wrinkles of the lower part of my face.
-1	I am dissatisfied with the wrinkles of the lower part of my face.
0	I am somewhat satisfied with the wrinkles of the lower part of my face.
+1	I am satisfied with the wrinkles of the lower part of my face.
+2	I am very satisfied with the wrinkles of the lower part of my face.

4.2.7. Secondary Efficacy Assessments

The pivotal Phase III clinical trials, IT-R-005 and IT-R-006, included secondary assessments of efficacy by both the subject and the Evaluator based on the comparison of photographs taken at baseline and at specific time points after administration of study treatment. The use of photographic assessments was included in order to capture the subject's and Evaluator's perception of the change in wrinkle appearance over time, which may not be captured in real time due to the gradual onset of treatment response. The scales used for the photographic assessment and the definition of a positive response to treatment are described in detail in Section 5.2.3, where the results of this secondary analysis are presented for the Integrated MITT Population.

4.2.8. Efficacy Endpoints

4.2.8.1. Co-Primary Endpoints

To determine whether the studies met their efficacy endpoints, subjects were categorized as "responders" or "non-responders" based on the change from baseline in the subject and the Evaluator assessment scores. A two point improvement was required to be considered a responder on the subject and Evaluator assessment scales. The Lemperle scale used for the Evaluator assessment has been validated to detect a one point improvement in the severity of the nasolabial fold wrinkle. However, because the assessment of appearance can be subjective and prone to variability, Isolagen agreed with FDA to define success for this endpoint as a two point improvement for each nasolabial

fold, i.e. for a given patient, both the left and right nasolabial fold had to improve by two points in the Evaluator's assessment in order to be considered a responder. A two point criterion for response was also applied to the subject assessment to provide greater assurance that subjects scored as responders had indeed experienced a positive response to treatment.

4.2.8.2. Secondary Endpoints

Secondary efficacy endpoints specified by the protocol included the percent response among Isolagen Therapy™-randomized subjects versus placebo-randomized subjects in the assessment of wrinkle improvement relative to baseline. Both the subject and the Evaluator compared photographs taken at Baseline and at specified study visits to rate the improvement in wrinkle appearance on a 5-point scale (Section 5.2.5). A positive response was defined as a rating of +1 ("better") or +2 ("much better") on the subject or Evaluator scales.

4.2.9. Sample Size

The sample size calculation for the pivotal clinical studies, IT-R-005 and IT-R-006, was based upon previous clinical experience. In previous clinical studies, specifically IT-R-003A and IT-R-003B, an Isolagen Therapy™ response of 40% and a placebo response of 20% were observed at the timepoint evaluated. Thus, a response rate of approximately 40% in Isolagen Therapy™ versus 20% in placebo were expected for the Evaluator's assessment in IT-R-005 and IT-R-006.

4.2.10. Safety Assessments

Isolagen Therapy™ has been tested for the treatment of facial rhytids including nasolabial folds in seven clinical studies (Table 2). The safety population for analysis included all subjects in these studies who received at least one treatment with Isolagen Therapy™ or placebo. Vital signs and adverse events were collected for all studies. Although clinical laboratory assessments were collected in the first two studies, IT-R-001 and IT-R-002, they were not collected in subsequent studies.

4.2.11. Safety Endpoints

The primary analyses for safety are based on treatment-emergent adverse events (TEAEs), defined as any adverse medical occurrence that begins or worsens on the first day of treatment administration or any day thereafter during the study period. AEs occurring after subject enrollment and biopsy and prior to the first treatment administration were recorded but have not been included in the integrated safety analysis.

The data provided in the initial BLA submitted to the FDA included integrated safety data collected for 6 months following treatment from studies IT-R-001, IT-R-002, IT-R-

003A, IT-R-003B, IT-R-005, IT-R-006, and IT-R-007. Twelve month safety data based on a scripted telephone contact has been collected and are summarized separately in this report (see Section 6.2).

5. EFFICACY OF ISOLAGEN THERAPY™

The adequate and well-controlled pivotal studies demonstrating effectiveness in support of the proposed label claim are the pivotal, Phase III, multicenter studies, IT-R-005 and IT-R-006, which were conducted concurrently under an identical single protocol in accordance with an FDA Special Protocol Assessment (SPA) agreement. Additional Phase III clinical studies (IT-R-002, IT-R-003A and IT-R-003B) provide supportive evidence of the effectiveness of Isolagen Therapy™ in the treatment of nasolabial fold wrinkles. The results for the primary efficacy endpoints from the individual pivotal studies are presented below, followed by a summary of additional secondary analyses of the integrated efficacy population from studies IT-R-005 and IT-R-006. The co-primary efficacy results of the supportive studies, IT-R-002, IT-R-003A and IT-R-003B are also presented.

5.1. PRIMARY EFFICACY RESULTS FROM IT-R-005 AND IT-R-006

The Phase III studies IT-R-005 and IT-R-006 demonstrated that Isolagen Therapy™ results in improvement of nasolabial fold wrinkles when evaluated by the subject or a blinded Evaluator. For both co-primary endpoints in both pivotal studies, the number of responders in the Isolagen Therapy™-treated group exceeded the number of responders in the placebo-treated group by a statistically significant margin (all p-values <0.01).

5.1.1. Efficacy Analysis Populations

Statistical analysis of the co-primary endpoints to evaluate the efficacy of Isolagen Therapy™ was performed on the Intent-to-Treat (ITT) population, which included all subjects who were randomized to study treatment, regardless of whether they received treatment. Additional supporting statistical analyses performed on the Modified Intent-to-Treat (MITT) population are presented in this briefing document. The MITT population included all subjects who were randomized to study treatment and received at least one treatment. Thus, this population excluded those subjects that were entered into the study and may have been biopsied, but did not receive an injection of placebo or Isolagen Therapy™. Table 5 summarizes the subjects included in each efficacy analysis population.

Table 5. Efficacy Analysis Populations

Population	Subjects Included
Intent-to-Treat (ITT)	Subjects who were randomized to study treatment. These subjects are summarized according to the group to which they were randomized, regardless of whether they received treatment.
Modified Intent-to-Treat (MITT)	Subjects who were randomized to study treatment and received at least one treatment.

5.1.2. Statistical Methods

The primary efficacy analysis was performed at 6 months following the third treatment (Visit 6). The primary statistical analysis of the co-primary endpoints was performed on the Intent to Treat population, which included all subjects who were randomized in the study, regardless of whether they received treatment. Subjects for whom Visit 6 data were not collected were considered treatment failures. For the study to be considered a success, a significant positive result was necessary for both the subject and Evaluator endpoints with a p-value less than or equal to 0.05. A Cochran-Mantel-Haenszel (CMH) test of general association stratified by study site was used to compare the overall response to Isolagen Therapy™ and placebo for both co-primary endpoints. Since the study must have met both endpoints to be considered significant, there was no additional adjustment due to multiplicity.

In addition, secondary statistical analyses of the two co-primary endpoints were performed on the MITT population (Table 5). Because the ITT population included subjects that were not treated, the analysis of the MITT population may more accurately reflect the efficacy of Isolagen Therapy™ for the treatment of nasolabial fold wrinkles. It should be noted that analysis of both the ITT and MITT populations for both endpoints were statistically significant.

5.1.3. Demographic and Baseline Characteristics

5.1.3.1. Demographics

The Baseline demographics of the ITT Populations of the individual IT-R-005 and IT-R-006 studies were very similar (Table 6). The majority of subjects in each study population were White (95% for IT-R-005 and 89% for IT-R-006) and female (90% for IT-R-005 and 91% for IT-R-006) with a mean age of 55 years (mean age of 56.7 years for IT-R-005 and 54.6 years for IT-R-006). There were approximately 10% Hispanic or Latino subjects in each study. Only 5 (1%) of the 421 subjects from both studies were Black. There were no significant demographic differences between the subjects randomized to the Isolagen Therapy™ or placebo group for either study.

Table 6. Subject Demographic Characteristics for the Pivotal Phase III Studies

	IT-R-005 ITT Population			IT-R-006 ITT Population		
	Treatment Group		Total (N=203)	Treatment Group		Total (N=218)
	Isolagen Therapy™ (N=100)	Placebo (N=103)		Isolagen Therapy™ (N=110)	Placebo (N=108)	
Age, years						
Mean (SD)	57.5 (8.32)	55.9 (7.87)	56.7 (8.12)	53.9 (10.38)	55.4 (9.42)	54.6 (9.92)
Median	57.0	56.0	56.0	55.0	55.0	55.0
Range	38, 75	35, 78	35, 78	23, 75	26, 81	23, 81
Baseline Age Group						
> 40 Years, ≤ 50 Years	19 (19%)	25 (24%)	44 (11%)	39 (35%)	34 (31%)	73 (33%)
> 50 Years, < 65 Years	60 (60%)	62 (60%)	122 (60%)	56 (51%)	55 (51%)	111 (51%)
≥ 65 Years	21 (21%)	16 (16%)	37 (18%)	15 (14%)	19 (18%)	34 (16%)
Gender						
Female	88 (88%)	94 (91%)	182 (90%)	103 (94%)	95 (88%)	198 (91%)
Male	12 (12%)	9 (9%)	21 (10%)	7 (6%)	13 (12%)	20 (9%)
Race/Ethnicity						
White	94 (94%)	99 (96%)	193 (95%)	98 (89%)	95 (88%)	193 (89%)
Black or African-American	1 (1%)	2 (2%)	3 (2%)	1 (<1%)	1 (<1%)	2 (<1%)
Asian	2 (2%)	0	2 (<1%)	0	0	0
Hispanic or Latino	10 (10%)	7 (7%)	17 (8%)	12 (11%)	12 (11%)	24 (11%)
American Indian or Alaska Native	0	1 (<1%)	1 (<1%)	0	0	0
Other	3 (3%)	1 (<1%)	4 (2%)	11 (10%)	12 (11%)	23 (11%)

In a survey of over 14,000 board-certified physicians specializing in plastic surgery, otolaryngology, and dermatology, the American Society of Aesthetic Plastic Surgery (ASAPS) found that, in 2007, 91% of cosmetic procedures were performed on women, 78% were performed on White subjects, and 72% were performed on subjects between 35 and 64 years of age with only 6% of procedures being performed on subjects over 65 years of age. Therefore, the demographic characteristics of these pivotal Phase III studies were well-matched with the demographics of the potential commercial market for Isolagen Therapy™.

5.1.3.2. Baseline Wrinkle Assessments

Baseline wrinkle severity as assessed by the subject and by the Evaluator is summarized by treatment group for studies IT-R-005 and IT-R-006 in Table 7. Eligibility criteria required that subjects be "Very Dissatisfied" or "Dissatisfied" on the Baseline Subject Wrinkle Assessment, and have a wrinkle severity of Grade 3 (Moderately Deep Wrinkle), Grade 4 (Deep Wrinkle), or Grade 5 (Very Deep Wrinkle) on the Baseline Evaluator Wrinkle Severity Assessment. All randomized subjects met these criteria.

At Baseline the majority of subjects in each of the pivotal studies' ITT Populations were very dissatisfied with the wrinkles in the lower part of their face (60 - 62%). Tests evaluating the homogeneity of distribution of Subject Wrinkle Assessments across treatment arms indicated that there was no significant difference between the Isolagen Therapy™- and placebo-randomized groups in either study at Baseline.

On the Evaluator Wrinkle Severity Assessment at Baseline the majority of subject's wrinkles in each study were assessed as Grade 3 (Moderately Deep Wrinkle) or Grade 4 (Deep Wrinkle) with the population approximately equally divided between these two categories. Tests evaluating the homogeneity of distribution of Evaluator Wrinkle Severity Assessments across treatment arms indicated that there was no significant difference between the Isolagen Therapy™- and placebo-randomized groups in either study at Baseline.

Table 7. Baseline Subject Wrinkle Assessment and Evaluator Wrinkle Severity Assessment for the Pivotal Phase III Studies

Individual Studies ITT Populations				
	IT-R-005		**IT-R-006**	
	Isolagen Therapy™ (N=100)	**Placebo (N=103)**	**Isolagen Therapy™ (N=110)**	**Placebo (N=108)**
Baseline Subject Wrinkle Assessment				
Very Dissatisfied (-2)	65 (65%)	61 (59%)	69 (63%)	62 (57%)
Dissatisfied (-1)	35 (35%)	42 (41%)	41 (37%)	46 (43%)
Baseline Evaluator Wrinkle Severity Assessment (Left Wrinkle)				
Grade 3	44 (44%)	51 (50%)	49 (45%)	43 (40%)
Grade 4	45 (45%)	40 (39%)	45 (41%)	52 (48%)
Grade 5	11 (11%)	12 (12%)	16 (15%)	13 (12%)
Baseline Evaluator Wrinkle Severity Assessment (Right Wrinkle)				
Grade 3	49 (49%)	53 (52%)	55 (50%)	45 (42%)
Grade 4	39 (39%)	38 (37%)	41 (37%)	53 (49%)
Grade 5	12 (12%)	12 (12%)	14 (13%)	10 (9%)

5.1.3.3. Length (cm) of Wrinkle Treatment

In Study IT-R-005 the total Baseline wrinkle length ranged from 6.2 to 16.0 cm for the Isolagen Therapy™ group and from 6.5 to 18.0 cm for the placebo group. Total Baseline wrinkle length in the IT-R-006 study ranged from 4.0 to 16.5 cm in the Isolagen Therapy™ group and from 4.0 to 17.0 cm in the placebo group. A Kruskal-Wallace test evaluating homogeneity of Baseline measurements across treatment arms revealed there was no statistically significant difference in Baseline wrinkle length between the Isolagen Therapy™ and placebo groups in either study (p-values of 0.4720 and 0.5818 for Studies IT-R-005 and IT-R-006, respectively).

In summary, randomization was successful in that subject demographics, baseline wrinkle severity, and length of treatment area were no different between the subjects randomized to Isolagen Therapy™ and subjects randomized to placebo in either study.

5.1.1. Subject Disposition

All randomized subjects (Isolagen Therapy™ or placebo) were included in the primary analysis of efficacy from the pivotal clinical studies, IT-R-005 and IT-R-006. A total of 421 subjects (210 Isolagen Therapy™ and 211 placebo) were randomized in both studies combined. Table 8 shows the percentage of all randomized subjects who completed each study or who terminated early from each study, and the reason for early termination, if applicable.

Table 8. Subject Disposition in Pivotal Studies IT-R-005 and IT-R-006

	IT-R-005 ITT Population, n (%)			IT-R-006 ITT Population, n (%)		
	Treatment Group		Total	Treatment Group		Total
	Isolagen Therapy™	Placebo		Isolagen Therapy™	Placebo	
Subjects Randomized (ITT population)	100	103	203	110	108	218
Subjects receiving at least one treatment (MITT population)	83 (83%)	92 (89%)	175 (86%)	98 (89%)	99 (92%)	197 (90%)
Study Completion Status						
Completed Study	80 (80%)	88 (85%)	168 (83%)	93 (85%)	98 (91%)	191 (88%)
Early Termination	20 (20%)	15 (15%)	35 (17%)	17 (15%)	10 (9%)	27 (12%)
Reason for Early Termination						
Subject withdrawal	6 (6%)	6 (6%)	12 (6%)	3 (3%)	4 (4%)	7 (3%)
Sponsor Request	5 (5%)	1 (<1%)	6 (3%)	10 (9%)	4 (4%)	14 (6%)
Adverse Event	2 (2%)	1 (<1%)	3 (2%)	1 (<1%)	1 (<1%)	2 (<1%)
Non-compliance with Protocol	3 (3%)	1 (<1%)	4 (2%)	2 (2%)	1 (<1%)	3 (1%)
Lost to follow-up	1 (1%)	3 (3%)	4 (2%)	0	0	0
Other	3 (3%)	3 (3%)	6 (3%)[a]	1 (<1%)	0	1 (<1%)[b]

Note: Denominator for percentages is the total number of subjects in the treatment group and/or population.
[a] "Other" includes history or diagnosis of basal cell carcinoma (5 subjects) and history of prolactin secreting tumor (1 subject).
[b]The subject terminated due to "Other" reason moved out of state.

In both studies, slightly more subjects randomized to placebo completed the study compared to subjects randomized to Isolagen Therapy™. Twenty percent (20%) and 15% of subjects randomized to Isolagen Therapy™ and placebo, respectively, terminated early from study IT-R-005 compared to 15% and 9%, respectively, for study IT-R-006. The majority of subjects who terminated early from the studies terminated after the Baseline Biopsy Visit, at which time subjects had been randomized, but prior to Treatment Visit 1. The major reasons for termination were Sponsor request (primarily for subjects for whom study product could not be manufactured within the timeframe stated in the protocol), and withdrawal of subject consent.

Three subjects were terminated from the study due to an adverse event (AE). One Isolagen Therapy™ subject was terminated from the study after Study Visit 1 due to moderate injection site pain. One subject was terminated from treatment due to a severe injection site reaction; this subject completed all follow-up visits. Both these events were considered by the investigator to be definitely related to study treatment. One placebo treated subject died of a heart attack after Visit 5; this AE was considered unrelated to study treatment. In study IT-R-006, two subjects were terminated from the study due to an adverse event. One subject, randomized to receive placebo, died of cardiac arrest prior to receiving study treatment; this event was considered by the Investigator to be unrelated to study treatment. Another subject, who received Isolagen Therapy™, was terminated after Study Treatment Two due to mild bruising associated with the injection; this event was considered by the Investigator to be definitely related to study treatment.

In both studies, a large majority of subjects who received one treatment also completed the study through Visit 6 (96% for IT-R-005 and 97% for IT-R-006).

5.1.2. Primary Efficacy Analysis Based on Co-Primary Endpoints

The co-primary efficacy endpoints for the pivotal clinical studies were the percentage of randomized subjects (ITT population) with a 2-point improvement on the Subject Wrinkle Assessment Scale and the percentage of subjects with a 2-point improvement for both nasolabial folds on the Evaluator Wrinkle Assessment Scale. The Subject Wrinkle Assessment Scale is a 5-point scale and the Evaluator Wrinkle Assessment Scale is a 6-point scale. The results for each of the co-primary efficacy endpoints in the Phase III pivotal studies, IT-R-005 and IT-R-006, are presented in Table 9.

A total of 203 subjects were randomized to study IT-R-005. One hundred (100) subjects were randomized to receive Isolagen Therapy™ and 103 subjects were randomized to receive placebo. All randomized subjects were included in the ITT Population (regardless of whether they received treatment). In this population, 57% of Isolagen Therapy™-treated subjects and 30% of placebo-treated subjects were responders as measured by the Subject Wrinkle Assessment six months after the third treatment. Based on the Evaluator Wrinkle Assessment, 33% of Isolagen Therapy™-treated subjects and

7% of placebo-treated subjects were responders when evaluated six months after the third treatment. The difference in response between treatment groups for both assessments was statistically significant with a p-value of less than 0.0001 (Table 9).

Similar results were obtained from the second pivotal Phase III study, IT-R-006. A total of 218 subjects were randomized to the study. One hundred ten (110) subjects were randomized to receive Isolagen Therapy™ and 108 subjects were randomized to receive placebo. Based on the Subject Wrinkle Assessment, 45% of Isolagen Therapy™-treated subjects and 18% of placebo-treated subjects were responders six months after the third treatment. For the co-primary Evaluator Wrinkle Assessment, 19% of Isolagen Therapy™-treated subjects and 7% of placebo-treated subjects were responders when assessed six months after the third treatment. Again, the difference between treatment groups was highly significant by both assessments, with p-values of less than 0.01 (Table 9). Thus, the co-primary efficacy endpoints for each pivotal clinical study, as agreed upon with the FDA, were met.

Table 9. Primary Efficacy Results for the ITT Population in Studies IT-R-005 and IT-R-006 (Co-Primary Endpoint Analyses)

	IT-R-005		IT-R-006	
	Isolagen Therapy™	**Placebo**	**Isolagen Therapy™**	**Placebo**
Subject Wrinkle Assessment				
Number of ITT Subjects	100	103	110	108
Number of Responders	57	31	50	19
Percent Responders	57%	30%	45%	18%
p-value	0.0001[a]		<0.0001[a]	
Evaluator Wrinkle Assessment				
Number of ITT Subjects	100	103	110	108
Number of Responders	33	7	21	8
Percent Responders	33%	7%	19%	7%
p-value	<0.0001[a]		0.0075[a]	

[a]Cochran-Mantel-Haenszel (CMH) test stratified by combined treatment site.

5.1.3. Secondary Efficacy Results for Modified Intent-to-Treat Population

The MITT population corresponded to randomized subjects who received at least one dose of study treatment (Table 5). Because the MITT population excluded subjects who received no treatment, the analysis of this population is more likely to reflect the efficacy of Isolagen Therapy™ relative to placebo for the treatment of nasolabial fold wrinkles. When the co-primary efficacy endpoints were evaluated for the MITT population, the

results remained highly significant for both endpoints in both studies. Based on the Subject Wrinkle Assessment at Visit 6 (six months after the third treatment visit), 69% of Isolagen Therapy™-treated subjects and 34% of placebo treated subjects were responders in study IT-R-005, while 51% of Isolagen Therapy™-treated subjects and 19% of placebo treated subjects were responders in study IT-R-006 (Table 10). For the Evaluator Wrinkle Assessment, 40% of Isolagen Therapy™-treated subjects and 8% of placebo-treated subjects were responders in study IT-R-005, while 21% of Isolagen Therapy™-treated subjects and 8% of placebo-treated subjects were responders in study IT-R-006 (Table 10). The difference in response between treatment groups was again highly statistically significant with a p-value of less than 0.01 for both endpoints in both studies.

Table 10. Efficacy Results for the MITT Population in Studies IT-R-005 and IT-R-006

	IT-R-005		IT-R-006	
	Isolagen Therapy™	**Placebo**	**Isolagen Therapy™**	**Placebo**
Subject Wrinkle Assessment				
Number of MITT Subjects	83	92	98	99
Number of Responders [a]	57	31	50	19
Percent Responders	69%	34%	51%	19%
p-value	<0.0001[b]		<0.0001[b]	
Evaluator Wrinkle Assessment				
Number of MITT Subjects	83	92	98	99
Number of Responders [a]	33	7	21	8
Percent Responders	40%	8%	21%	8%
p-value	<0.0001[b]		0.0037[b]	

[a]Non-completers treated as failures; primary efficacy evaluation imputation method.
[b]CMH test stratified by combined treatment site.

5.2. SECONDARY ANALYSES OF EFFICACY IN IT-R-005 AND IT-R-006

Additional efficacy analyses were performed on the integrated populations from both pivotal studies, (i.e. the populations of IT-R-005 and IT-R-006 were combined), to further evaluate the timing and extent of subject response to Isolagen Therapy™ versus placebo, and the relative response rates in subpopulations. The results of these secondary analyses are presented below for the MITT population, which most accurately reflects the comparative response rates to Isolagen Therapy™ and placebo in subjects who received at least one dose of study treatment.

5.2.1. Efficacy Analysis of Integrated MITT Population

The co-primary efficacy endpoints for the pivotal studies were the percentage of subjects with a two-point improvement at Visit 6 (six months after the third treatment administration) as compared to Baseline on the Subject Wrinkle Assessment and the percentage of subjects with a two-point improvement for both nasolabial fold wrinkles at Visit 6 as compared to Baseline on the Evaluator Wrinkle Severity Assessment.

The proportion of responders in the Integrated MITT population is presented in Table 11 for the Subject Wrinkle Assessment and in Table 12 for the Evaluator Wrinkle Assessment. The tables show the percentage of responders at Visit 3 (immediately prior to the third treatment), Visit 4 (two months after the third treatment), Visit 5 (four months after the third treatment) and Visit 6 (six months after the third treatment). Subjects who did not complete their efficacy assessment at any visit were treated as non-responders for that visit.

Forty percent (40%) of Isolagen Therapy™-treated subjects met the criteria for response to treatment for the Subject Wrinkle Assessment at Visit 3, after only two administrations of Isolagen Therapy™, compared to 23% percent of placebo-treated subjects. The percentage of responders in the Isolagen Therapy™ treatment group increased noticeably to 55% by two months after the third treatment, then showed a further modest increase to 59% by six months after the third treatment. There was no significant increase for placebo-treated subjects after Visit 3, of whom 26% were responders at each of Visits 4 through 6. The difference in response rate between the Isolagen Therapy™ and placebo treatment groups was statistically significant at all assessment visits, with p-values of 0.0001 or below (Table 11).

Similarly, for the Evaluator Wrinkle Assessment, 17% of Isolagen Therapy™-treated subjects had responded after two treatments (Visit 3), compared to 5% of placebo-treated subjects (Table 12). As for the subject assessment, the percentage of responders in the Isolagen Therapy™ treatment group increased noticeably by two months after the third treatment (Visit 4) to 28%, reaching 30% by four months after the third treatment (Visit 6). Responders in the placebo treatment group increased to 9% by Visit 4 and remained stable thereafter. The differences in response rate between the treatment groups was again highly significant at all assessment visits (p-value <0.0001).

Table 11. Subject Wrinkle Assessment at Visits 3, 4, 5 and 6 for the Integrated MITT Population (IT-R-005 and IT-R-006 Combined)

	Visit 3 (Prior to Third Treatment)		Visit 4 (Two Months after Third Treatment)		Visit 5 (Four Months after Third Treatment)		Visit 6 (Six Months after Third Treatment)	
	IT[a]	Placebo	IT	Placebo	IT	Placebo	IT	Placebo
Number of MITT Subjects	181	191	181	191	181	191	181	191
Number of Responders	72	43	100	50	95	50	107	50
Percent Responders	40%	23%	55%	26%	52%	26%	59%	26%
p-value	0.0001[b]		<0.0001[b]		<0.0001[b]		<0.0001[b]	

[a]Isolagen Therapy™
[b]Fisher's Exact test

Table 12. Evaluator Wrinkle Assessment at Visits 3, 4, 5 and 6 for the Integrated MITT Population (IT-R-005 and IT-R-006 Combined)

	Visit 3 (Prior to Third Treatment)		Visit 4 (Two Months after Third Treatment)		Visit 5 (Four Months after Third Treatment)		Visit 6 (Six Months after Third Treatment)	
	IT[a]	Placebo	IT	Placebo	IT	Placebo	IT	Placebo
Number of MITT Subjects	181	191	181	191	181	191	181	191
Number of Responders	31	9	50	18	53	16	54	15
Percent Responders	17%	5%	28%	9%	29%	8%	30%	8%
p-value	<0.0001[b]		<0.0001[b]		<0.0001[b]		<0.0001[b]	

[a]Isolagen Therapy™
[b]Fisher's Exact test

Overall, a majority of the MITT patient population participating in the pivotal Phase III studies showed a shift on the Subject Wrinkle Assessment Scale from being "very dissatisfied" or "dissatisfied" with the appearance of the lower region of their face to being "somewhat satisfied," "satisfied" or "very satisfied" (Figure 4). Note that subjects

with Baseline assessments of "somewhat satisfied," "satisfied" or "very satisfied" were excluded from participation in the study.

Figure 4. Subject Assessment at Baseline and Visit 6 (Six Months after Last Treatment Visit) for Integrated MITT Population

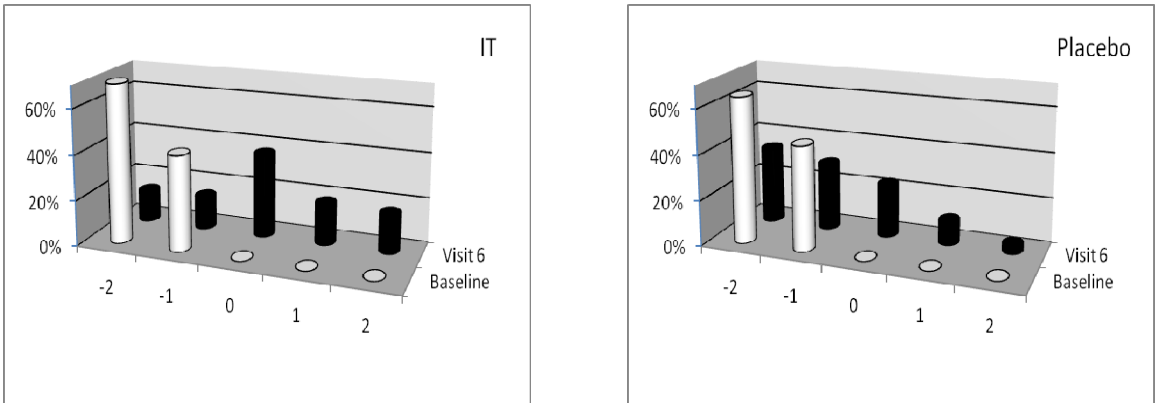
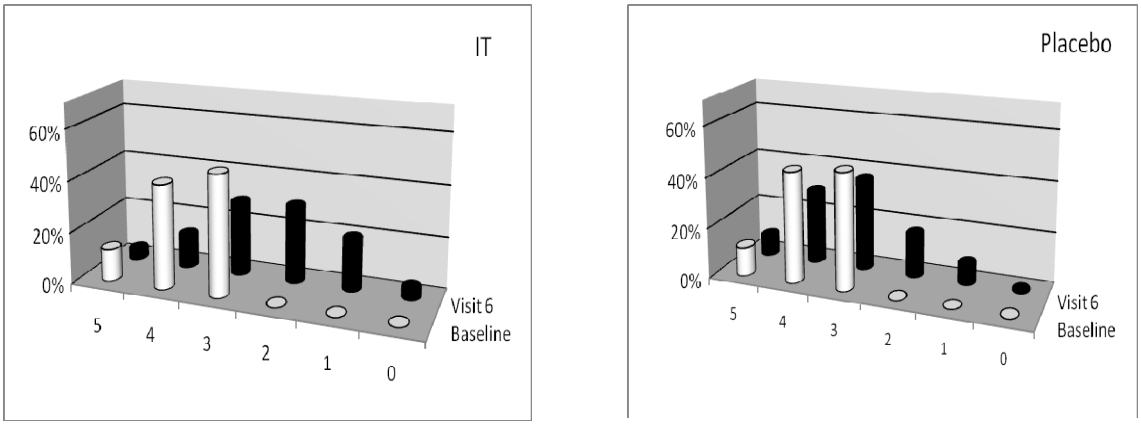


Figure 5 displays the shifts in Evaluator Wrinkle Assessment scores for the Integrated MITT Population for studies IT-R-005 and IT-R-006. It is noteworthy that many subjects with the most severe baseline assessment score of 5 ("very deep wrinkle") experienced improvement following Isolagen Therapy™ treatment. A greater percentage of Isolagen Therapy™-treated subjects than placebo-treated subjects with the "very deep wrinkle" baseline classification experienced improvement.

Figure 5. Evaluator Assessment at Baseline and Visit 6 (Six Months after Last Treatment Visit) for Integrated MITT Population



5.2.2. Secondary Efficacy Analysis based on 1-Point Improvement on Primary Assessment Scales

Although the primary efficacy analyses required a 2-point improvement on the Subject and Evaluator Wrinkle Assessment Scales to qualify as a response to treatment, a 1-point improvement on either scale may, in fact, have clinical significance to the patient. Table 13 and Table 14 present the percentage of subjects who were responders at each assessment visit using the criterion that a 1-point improvement constituted a positive response.

At Visit 6, six months after the third treatment visit, the proportion of subjects in the Integrated MITT Population who were responders based on a 1-point improvement in the Subject Wrinkle Assessment was 78% for Isolagen Therapy™-treated subjects and 48% for placebo-treated subjects (Table 13). This difference was statistically significant, with a p-value of <0.0001. Significantly, even at Visit 3, prior to the third treatment, a large proportion (70%) of subjects were responders in the Isolagen Therapy™-treated group versus 52% in the placebo-treated group (p-value = 0.0002).

Similarly, the proportion of responders at Visit 6 on the Evaluator Wrinkle Severity Assessment, where response is defined as a one-point bilateral improvement in nasolabial folds, was 64% for the Isolagen Therapy™-treated subjects and 36% for the placebo-treated subjects (p-value < 0.0001; Table 14). At Visit 3, prior to the third treatment, 53% of Isolagen Therapy™-treated subjects were responders versus 32% of placebo-treated subjects (p-value < 0.0001).

These data indicate that a clinically-meaningful response to Isolagen Therapy™ was observed by both the subject and the blinded Evaluator as early as 10 weeks (Visit 3) following the initiation of Isolagen Therapy™ treatment in a large majority of subjects.

Table 13. Subject Wrinkle Assessment for Subjects with One-Point Improvement at Visits 3, 4, 5 and 6 for the Integrated MITT Population

	Visit 3 (Prior to Third Treatment)		Visit 4 (Two Months after Third Treatment)		Visit 5 (Four Months after Third Treatment)		Visit 6 (Six Months after Third Treatment)	
	IT[a]	Placebo	IT	Placebo	IT	Placebo	IT	Placebo
Number of MITT Subjects	181	191	181	191	181	191	181	191
Number of Responders	127	100	137	105	133	101	142	92
Percent Responders	70%	52%	76%	55%	73%	53%	78%	48%
p-value	0.0002[b]		<0.0001[b]		<0.0001[b]		<0.0001[b]	

[a]Isolagen Therapy™
[b]Fisher's Exact test

Table 14. Evaluator Wrinkle Assessment for Subjects with One-Point Bilateral Improvement on at Visits 3, 4, 5 and 6 for the Integrated MITT Population

	Visit 3 (Prior to Third Treatment)		Visit 4 (Two Months after Third Treatment)		Visit 5 (Four Months after Third Treatment)		Visit 6 (Six Months after Third Treatment)	
	IT[a]	Placebo	IT	Placebo	IT	Placebo	IT	Placebo
Number of MITT Subjects	181	191	181	191	181	191	181	191
Number of Responders	96	62	114	73	118	71	116	68
Percent Responders	53%	32%	63%	38%	65%	37%	64%	36%
p-value	<0.0001[b]		<0.0001[b]		<0.0001[b]		<0.0001[b]	

[a]Isolagen Therapy™
[b]Fisher's Exact test

5.2.3. Secondary Efficacy Analysis based on Photographic Comparisons

The primary efficacy endpoints were based on the results of a live assessment of the subject's wrinkles by the subject or the Evaluator at a specified visit compared to the Baseline live assessment. In addition, a secondary endpoint measured the Evaluator and subject's opinion of the improvement or decline of the treated nasolabial fold wrinkles at a specified visit, as compared to Baseline, using photographs taken at each visit.

At Visit 6, the Evaluator and the Subject were instructed to rate the photographs for each of Visits 3 through 6 (zero, two, four or six months after the last treatment visit) relative to a photograph taken at Baseline. The Evaluator assessed the left and right nasolabial fold wrinkles separately. The Evaluator or the subject was instructed to select the score on a 5-point ordinal scale (Table 15) which best described the photographs from each visit. The Evaluators rated the wrinkles themselves, while the subjects rated their appearance. A positive response by either assessment was defined as a score of +1 or +2 at the specified visit.

Table 15. Secondary Evaluator and Subject Assessment Scales of Wrinkle Improvement from Baseline based on Photographic Comparisons

Wrinkle Improvement Score	Evaluator Description of Improvement	Subject Description of Improvement
-2	Wrinkle is much worse than before	Appearance is much worse than before
-1	Wrinkle is worse than before	Appearance is worse than before
0	Wrinkle is the same as before	Appearance is the same as before
+1	Wrinkle is better than before	Appearance is better than before
+2	Wrinkle is much better than before	Appearance is much better than before

The results of the Subject and Evaluator Improvement Assessments for the Integrated Efficacy MITT population are presented in Table 16 and Table 17, respectively, for the Visit 6 photographic comparison to Baseline. Subjects randomized to Isolagen Therapy™ had a statistically significantly higher response rate on the Subject Improvement Assessment (67%) than did subjects randomized to placebo (26%) with a p-value of less than 0.0001 (Table 16). When only those subjects that completed all three treatments were included, 71% of the Isolagen Therapy™-treated subjects were responders compared to 26% of the placebo-treated subjects (data not shown).

Table 16. Subject Photographic Improvement Assessment at Visit 6 for the Integrated MITT Population

	Treatment Group	
	Isolagen Therapy™	**Placebo**
Subject Improvement Assessment		
Number of MITT Subjects	181	191
Number of Responders	121	49
Percent Responders	67%	26%
p-value	<0.0001[a]	

[a]Fisher's Exact test

In Table 17, the Evaluator Improvement Assessment at Visit 6 is presented for the Integrated Efficacy MITT Population. Subjects randomized to Isolagen Therapy™ had a statistically significantly higher response rate for both the left and right nasolabial fold wrinkles (57% and 59%, respectively) than did subjects randomized to placebo (20% and 21% for the left and right nasolabial fold wrinkles, respectively) with p-values of less than 0.0001. When only those subjects who completed three treatments were included, 61% and 63% of Isolagen Therapy™-randomized subjects responded on the left and right nasolabial folds, respectively, compared to 21% and 22% of placebo-randomized subjects (data not shown).

Table 17. Evaluator Photographic Improvement Assessment at Visit 6 for the Integrated MITT Population

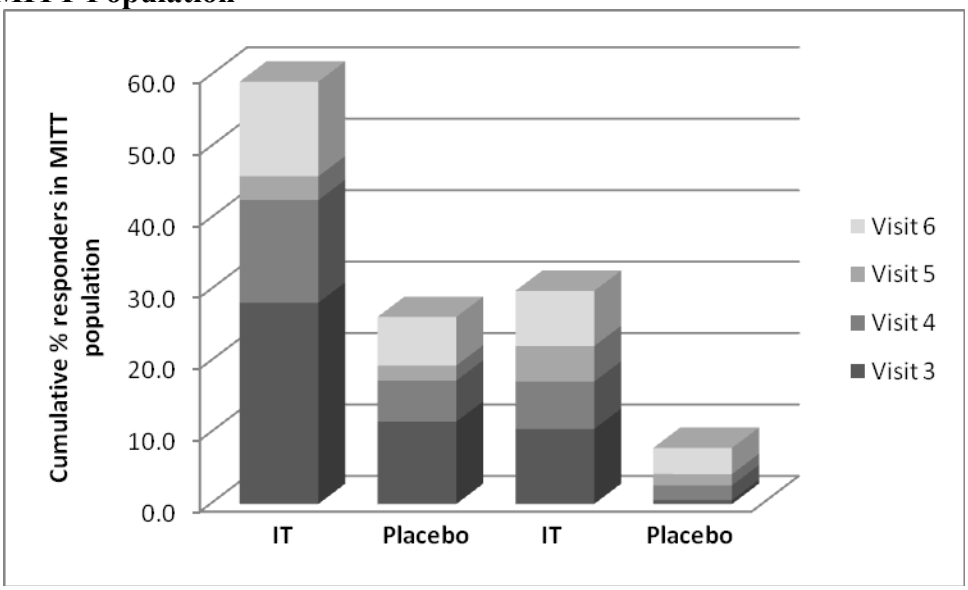
	Treatment Group	
	Isolagen Therapy™	**Placebo**
Left Nasolabial Fold Wrinkle		
Number of MITT Subjects	181	191
Number of Responders	104	39
Percent Responders	57%	20%
p-value	<0.0001[a]	
Right Nasolabial Fold Wrinkle		
Number of MITT Subjects	181	191
Number of Responders	107	41
Percent Responders	59%	21%
p-value	<0.0001[a]	

[a]Fisher's Exact Test.

5.2.4. Time to Onset of Sustained Response

Isolagen Therapy™ is not a therapy that is intended to provide an immediate benefit. Rather, wrinkle improvement from Isolagen Therapy™ appears to "build over time." This phenomenon is illustrated in Figure 6, which shows the cumulative increase in the percentage of subjects with a "sustained response" at each assessment visit. A "sustained response" was defined as a response that maintained a 2-point improvement from the time of the initial response through all subsequent evaluation visits. For example, a subject that had a positive response at Visit 3 and at Visit 6, but not at Visits 4 and 5, would not be counted as having a sustained response until Visit 6.

Figure 6. Cumulative Percentage of Subjects with Sustained Response in Integrated MITT Population



5.2.5. Duration of Effect

Due to the gradual onset of Isolagen Therapy™ response, many subjects were not categorized as responders by the study criteria until relatively late in the follow-up period (4-6 months after the third treatment). Therefore, the duration of Isolagen Therapy™ effect was not fully evaluated by the pivotal study design. However, since some subjects responded with a two point move as early as Visit 3 (after only two treatments), duration of response out to Visit 6 (total of 6 months after Visit 3) could be analyzed. Table 18 summarizes the percent sustained responders at 6 months after response. Of the 72 subjects who had responded based on the Subject Wrinkle Assessment at Visit 3, 71% experienced a sustained response through Visit 6 (six-month follow-up visit) compared to 51% of Visit 3 responders in the placebo group. For the Evaluator Wrinkle Assessment, a sustained response through Visit 6 was observed for 61% of Isolagen Therapy™-treated subjects compared to 11% of placebo-treated subjects.

Table 18. Visit 6 Response Data for Subjects Responding at Visit 3 (After Two Treatments)

	Subject Assessment		Evaluator Assessment	
	Isolagen Therapy™	**Placebo**	**Isolagen Therapy™**	**Placebo**
Number of responders at Visit 3	72	43	31	9
Responders remaining at Visit 6 (Six Month Follow-up Visit)	51	22	19	1
Percentage remaining at Visit 6	71%	51%	61%	11%

Although not intended as a formal assessment of efficacy, subjects who were contacted by telephone for the purposes of a 12-month safety follow-up in studies IT-R-005 and IT-R-006 were also asked to rate their opinion on the improvement or worsening of the appearance of the treated areas in the lower part of their face since their last study visit. Three hundred forty-six (346) of the 359 subjects in the long-term safety population (subjects who had received at least one treatment and completed the final clinic visit) responded to the phone interview, 173 in the Isolagen Therapy™-treated group and 186 in the placebo-treated group. Table 19 shows the responses by treatment group for those subjects who were identified as responders based on the Subject Wrinkle Assessment six months after their last treatment, and separately, for those subjects who were identified as non-responders by the Subject Wrinkle Assessment at the same time point. Subjects who did not complete the phone interview or who had received any cosmetic procedure to the face since the final clinic visit are listed separately in the table and are not included in the tabulation of responses.

Of the subjects who were responders at their final clinic visit, and who did not report any cosmetic procedures to the face since that visit, 99% of Isolagen Therapy™-treated subjects and 98% of placebo-treated subjects considered the appearance of their treated areas to be the same or better than at the final assessment, compared to 89% of Isolagen Therapy™-treated subjects and 91% of placebo-treated in the group who were non-responders at the final clinic visit (Table 19). Subjects who were non-responders at the final clinic visit were more likely than responders to assess their wrinkle appearance as worse at the 12-month follow-up call. While these data do not reflect an assessment based on a validated scale, they suggest that the responses observed at the final clinic visit (Visit 6) may be durable through at least 12 months. Further, subjects in the Isolagen Therapy™-treated group were more likely than subjects in the placebo-treated group to report the appearance of their treated area as better than at the final clinic visit, particularly for the subjects who were not considered responders at the final clinic visit. Among the latter subjects, 21% in the Isolagen Therapy™-treated group compared to 6% in the placebo-treated group considered their appearance to be better (Table 19). This suggests that the effect of Isolagen Therapy™ may continue to increase in some subjects

beyond the period evaluated in the clinical trial. It should be emphasized that at the time of the 12-month follow-up call, subjects remained blinded to their study treatment.

Table 19. Preliminary Analysis of Subject Opinion at 12 Months regarding Improvement or Worsening of Treated Areas since Last Study Visit (IT-R-005 and IT-R-006 Combined)

	Subject Response at 12 Months[a]; n (%)			
	Responders at Visit 6 (6-month follow-up visit)[b]		**Non-responders at Visit 6 (6-month follow-up visit)[b]**	
	Isolagen Therapy™ (N=107)	**Placebo (N=50)**	**Isolagen Therapy™ (N=65)**	**Placebo (N=137)**
No data (n)	3	1	5	4
Cosmetic procedures since last clinic visit (n)	9	6	13	20
All other subjects (n)	95	43	47	113
Appearance is worse than before last study visit (n, %)[c]	1 (1%)	1 (2%)	5 (11%)	10 (9%)
Appearance is the same as before last study visit (n, %)[c]	58 (61%)	30 (70%)	32 (68%)	96 (85%)
Appearance is better than before last study visit (n, %)[c]	36 (38%)	12 (28%)	10 (21%)	7 (6%)

[a]Where two answers were provided by a subject (e.g., same/better), the response corresponding to the more negative result was selected.
[b]Response/on-response based on Subject Wrinkle Assessment Scale
[c]Percentage of subjects with 12 month data and no reported cosmetic procedures to the face since last clinic visit

5.2.6. Evaluation of Efficacy in Subpopulations

Additional variables, including age, race and sex, were analyzed for their potential impact on the efficacy of Isolagen Therapy™. Because a large majority of enrolled subjects were female, White and less than 65 years of age, there were only limited data available for subjects in other demographics and no statistically significant differences were observed for any of these variables. A brief summary of the results for these subpopulations are presented in the following sections.

5.2.6.1. Age Groups

The proportion of responders, where response is defined as a two-point improvement, on the Subject Wrinkle Assessment was evaluated by age group (≤ 50, > 50 and < 65, and ≥ 65 years of age) for the Integrated Efficacy ITT Population. Based on the Subject Wrinkle Assessment at Visit 6, Isolagen Therapy™ response was 59%, 52%, and 36% in

subjects less than or equal to 50 years of age, subjects greater than 50 and less than 65 years of age, and subjects greater than or equal to 65 years of age, respectively (Table 20). Although there was a trend toward decreased efficacy with increased age, it was not statistically significant, with a Chi-Square p-value of 0.57 for comparison of response versus non-response in Isolagen Therapy™-treated subjects by age group. Placebo response did not show a similar trend with 19% placebo response in subjects of 50 or fewer years, 28% in subjects of 50 to 65 years, and 17% in subjects of more than 65 years (Table 20). The differences between subgroups were not statistically significant (Chi-Square p-value of 0.31 for comparison of response versus non-response in placebo-treated subjects by age group). The placebo results suggested that there was not a bias toward younger subjects assessing themselves more positively than older subjects.

For the Evaluator Assessment, Isolagen Therapy™ response was 30%, 28%, and 11% in subjects less than or equal to 50 years of age, subjects greater than 50 and less than 65 years of age, and subjects greater than or equal to 65 years of age, respectively (Table 20). The observed trend toward decreased efficacy with increased age was not statistically significant with a Chi-Square p-value of 0.74 for comparison of response versus non-response in Isolagen Therapy™-treated subjects by age group. A similar, though less marked trend was observed in placebo response with 6% placebo response in subjects of 50 or fewer years and 7% in subjects of 50 to 65 years, and 9% in subjects of more than 65 years (not statistically significant; Chi-Square p-value of 0.74 for comparison of response versus non-response in placebo-treated subjects by age group). This suggested that there may have been a slight bias toward Evaluators assessing younger subjects more positively than older subjects.

Overall, due to the small number of subjects over the age of 65 years, definitive conclusions cannot be drawn regarding the efficacy of Isolagen Therapy™ in the geriatric population.

Table 20. Co-Primary Efficacy Assessments at Visit 6 by Age Group for the Integrated Efficacy ITT Population

	Subject Wrinkle Assessment		Evaluator Wrinkle Assessment	
	Isolagen Therapy™	Placebo	Isolagen Therapy™	Placebo
≤ 50 Years of Age				
Number of ITT Subjects	46	54	46	54
Number of Responders	27	10	14	3
Percent Responders	59%	19%	30%	6%
>50 to <65 Years of Age				
Number of ITT Subjects	128	122	128	122
Number of Responders	66	34	36	9
Percent Responders	52%	28%	28%	7%
≥ 65 Years of Age				
Number of ITT Subjects	36	35	36	35
Number of Responders	13	6	4	3
Percent Responders	36%	17%	11%	9%

5.2.6.2. Sex

The proportion of responders based on the Subject Wrinkle Assessment and the Evaluator Wrinkle Assessment was analyzed by sex [male (n=41) and female (n=380)] for the Integrated Efficacy ITT Population (Table 21).

Isolagen Therapy™ response on the Subject Wrinkle Assessment at Visit 6 was 50% in female subjects and 53% in male subjects. There was not a statistically significant difference in response for female and male subjects (Chi-Square p-value of 0.52 for comparison of response versus non-response in Isolagen Therapy™-treated subjects by sex). Placebo response was 24% in female subjects and 23% in male subjects, which was not statistically significantly different (Chi-Square p-value of 0.57 for comparison of response versus non-response in placebo-treated subjects by sex).

Results of the Evaluator assessments sub-group analysis were also not significantly different between female and male subjects (Table 21). In females, 27% of Isolagen Therapy™-randomized subjects and 7% of placebo-randomized subjects were responders on the Evaluator Wrinkle Severity Assessment at Visit 6. In male subjects, the Isolagen Therapy™ response was 16% (lower than the female response rate) and the placebo

response was 9% (similar to that observed in females). There were no statistically significant differences in response based on sex of the subject (Chi-Square p-value of 0.23 for evaluation of response versus non-response in Isolagen Therapy™-treated subjects by sex, and Chi-Square p-value of 0.48 for evaluation of response versus non-response in placebo-treated subjects by sex).

Although there was no statistical difference in response rates between males and females, no conclusion can be drawn at this time regarding the relative efficacy of Isolagen Therapy™ between sex groups due to the limited number of male subjects enrolled in the study population.

Table 21. Co-Primary Efficacy Assessments at Visit 6 by Sex for the Integrated Efficacy ITT Population

	Subject Wrinkle Assessment		Evaluator Wrinkle Assessment	
	Isolagen Therapy™	**Placebo**	**Isolagen Therapy™**	**Placebo**
Females				
Number of ITT Subjects	191	189	191	189
Number of Responders	96	45	51	13
Percent Responders	50%	24%	27%	7%
Males				
Number of ITT Subjects	19	22	19	22
Number of Responders	10	5	3	2
Percent Responders	53%	23%	16%	9%

5.2.6.3. Race

The proportion of responders based on the Subject Wrinkle Assessment and the Evaluator Wrinkle Assessment was analyzed by race [white (n=371) and non-white (n=50)] for the Integrated Efficacy ITT Population (Table 22).

Isolagen Therapy™ response on the Subject Wrinkle Assessment at Visit 6 was higher in non-White subjects (63%) than in White subjects (49%). Similarly, placebo response was higher in non-White subjects (35%) than in White subjects (22%). The difference in treatment response between racial groups was not statistically significant (Chi-Square p-value of 0.118 for an evaluation of response versus non-response in Isolagen Therapy™-treated subjects by White versus non-White categorization; Chi-Square p-value of 0.144 in placebo-treated subjects). These data suggest that White and non-White subjects respond equally well to Isolagen Therapy™ treatment. Although the differences between the racial groups were not statistically significant, the higher response rates for non-

Whites compared to Whites for both Isolagen Therapy™ and placebo suggest that non-White subjects may assess themselves more positively than White subjects or that the placebo effect, which may be attributed to wound healing processes, may be longer lived in non-White subjects.

Table 22. Co-Primary Efficacy Assessments at Visit 6 by Race for the Integrated Efficacy ITT Population

	Subject Wrinkle Assessment		Evaluator Wrinkle Assessment	
	Isolagen Therapy™	**Placebo**	**Isolagen Therapy™**	**Placebo**
White				
Number of ITT Subjects	183	188	183	188
Number of Responders	89	42	43	13
Percent Responders	49%	22%	23%	7%
Non-White				
Number of ITT Subjects	27	23	27	23
Number of Responders	17	8	11	2
Percent Responders	63%	35%	41%	9%

In White subjects, 23% of Isolagen Therapy™-randomized subjects and 7% of placebo-randomized subjects were responders on the Evaluator Wrinkle Severity Assessment at Visit 6. In non-White subjects, the Isolagen Therapy™ response rate was 41% (higher than in White subjects) and the placebo response was 9% (approximately the same as White subjects). There were no statistically significant differences for response versus non-response for Isolagen Therapy™-treated subjects (Chi-Square p=0.0505) by racial analysis (White versus non-White), or for placebo-treated subjects (Chi-Square p=0.505). However, since the p-value for response versus non-response for Isolagen Therapy™-treated subjects by racial analysis (0.0505) is so close to the threshold for statistical significance, these data may suggest that Isolagen Therapy™ may be more efficacious in non-White subjects than in White subjects. However, the population of non-White subjects is small and additional investigation into the efficacy of Isolagen Therapy™ in this population would be necessary to determine the veracity of these results.

5.3. IT-R-005 AND IT-R-006 RESPONSE RATES BY SITE

Some variability was noted in the co-primary efficacy response rates between sites for the Subject Wrinkle Assessment (Table 23) and the Evaluator Wrinkle Assessment (Table 24). However, due to the relatively small number of subjects at each site, the significance

of this variability is unclear. A number of factors, including variability in injection technique, variability in the use of the assessment scales, and variability in the enrolled subject population could influence the outcome at each site. No one factor has been identified that clearly correlates with the site-to-site variability observed.

Table 23. Subject Wrinkle Assessment Responders at Visit 6 by Site for the ITT Populations from both Pivotal Studies

	Treatment Group	
	Isolagen Therapy™	**Placebo**
Overall	**107/210 (51%)**	**50/211 (24%)**
Site 5a	15/25 (60%)	9/24 (38%)
Site 5b	6/10 (60%)	4/11 (36%)
Site 5c	9/21 (43%)	5/20 (25%)
Site 5d	7/7 (100%)	3/8 (38%)
Site 5e	5/9 (56%)	3/10 (30%)
Site 5f	12/21 (57%)	6/22 (27%)
Site 5g	3/7 (43%)	1/8 (13%)
Site 6a	11/19 (58%)	4/17 (24%)
Site 6b	7/13 (54%)	2/16 (13%)
Site 6c	13/22 (59%)	1/22 (5%)
Site 6d	6/18 (33%)	5/17 (29%)
Site 6e	7/18 (39%)	3/17 (18%)
Site 6f	6/20 (30%)	4/19 (21%)

Table 24. Evaluator Wrinkle Severity Assessment Responders at Visit 6 by Site for the Integrated ITT Population

	Treatment Group	
	Isolagen Therapy™	**Placebo**
Overall	**54/210 (26%)**	**15/211 (7%)**
Site 5a	5/25 (20%)	1/24 (4%)
Site 5b	2/10 (20%)	1/11 (9%)
Site 5c	8/21 (38%)	1/20 (5%)
Site 5d	4/7 (57%)	0/8 (0%)
Site 5e	3/9 (33%)	1/10 (10%)
Site 5f	7/21 (33%)	1/22 (5%)
Site 5g	3/7 (43%)	1/8 (13%)
Site 6a	1/19 (5%)	2/17 (12%)
Site 6b	5/13 (39%)	2/16 (13%)
Site 6c	1/22 (5%)	0/22 (0%)
Site 6d	5/18 (28%)	2/17 (12%)
Site 6e	7/18 (39%)	2/17 (12%)
Site 6f	2/20 (10%)	0/19 (0%)

5.4. SUPPORTIVE EFFICACY DATA

In addition to the pivotal clinical studies, IT-R-005 and IT-R-006, the efficacy of Isolagen Therapy™ for the treatment of facial contour deformities was evaluated in three additional Phase III clinical trials. In each of these studies, Isolagen Therapy™ was administered in three treatments of 1.0 - 2.0 x 10^7 cells/mL. Differences between the supportive Phase III studies and the pivotal studies included the interval between treatments, the timing of efficacy assessments relative to the treatment schedule, and the scales used for the Investigator or subject assessment. The primary efficacy results from each of the supportive clinical studies are presented below.

5.4.1. Phase III Study IT-R-002

Study IT-R-002 was a randomized, double-blind, placebo-controlled study of Isolagen Therapy™ in 151 subjects (112 treated with Isolagen Therapy™ and 39 treated with placebo). In this study, treatments could be administered to multiple areas of the face including facial rhytids or scars, with one treatment area selected for the primary efficacy assessment. Three treatments were administered with an interval of 14 ± 7 days. The primary efficacy endpoint was based upon the Investigator's assessment of the primary

treatment area using a 7-point ordinal scale with a photoguide at four months after the initial treatment. Analysis of the primary efficacy assessment revealed a statistically significant difference in the proportion of responders between the Isolagen Therapy™-treated subjects (49.5%) and placebo-treated subjects (25.0%) (p-value = 0.0067, Cochran-Mantel-Haenszel test). Additionally, a number of secondary efficacy endpoints based upon alternative assessments by the Investigator, the subject, or an independent blinded Evaluator, were successfully met at four months. At six months following the initial treatment, all efficacy endpoints demonstrated statistically significant results. In the long-term phase of the study (12 months after the initial treatment), the primary efficacy endpoint, as well as a number of secondary efficacy endpoints, demonstrated a sustained response for the subjects treated with Isolagen Therapy™. These data provided early clinical evidence of the effectiveness of Isolagen Therapy™ for treatment of facial rhytids. The results of study IT-R-002 were provided to the FDA as data supportive of the efficacy of Isolagen Therapy™ for the treatment of nasolabial fold wrinkles.

5.4.2. Phase III Studies IT-R-003A and IT-R-003B

Studies IT-R-003A and IT-R-003B were conducted at six sites in the United States to determine the safety and efficacy of Isolagen Therapy™ injections for the treatment of facial contour deformities, specifically, nasolabial fold wrinkles and glabellar lines. The two studies were conducted according to an identical protocol that was developed in coordination with the FDA under a Special Protocol Assessment. Each subject was to receive three treatments of Isolagen Therapy™ at a dose of approximately 2.0×10^7 cells/mL administered every seven to 14 days. The efficacy of Isolagen Therapy™ was evaluated based on assessment of the primary treatment area at six months after the first treatment compared to baseline by both the blinded Investigator and the subject. The Investigator's assessment of wrinkle severity was based on a 6-point ordinal scale accompanied by a photoguide (Lemperle, 2001), where a positive response to treatment was defined as a 2-point improvement relative to the Baseline wrinkle severity score. The subject's assessment was based on a Visual Analog Scale (VAS) which ranged from 0 (no defect) to 100 (very severe defect). The co-primary endpoints were the proportion of responders in each treatment group based on the Investigator's assessment and the mean change from Baseline in the subjects' VAS scores at six months after the first treatment.

The design of studies IT-R-003A and -003B differed from the design of the pivotal clinical trials in several important ways, as outlined in Table 25.

Table 25. List of Significant Protocol Design Differences between Studies IT-R-003A/003B and Pivotal Studies IT-R-005/006

Protocol Element	Studies 003A/003B	Studies IT-R-005/006
Total allowable dose	1.0 mL/treatment*	2.0 mL/treatment*
	*Note: The cell concentration (1.0-2.0 x 10^7 cells/mL) and dose per linear cm (0.1 mL/cm) were not changed	
Treatment area	Treatment areas included nasolabial folds and glabellar lines	Treatment area was restricted to both nasolabial folds
Definition of "responder" on 6-point ordinal Evaluator assessment scale	2-point improvement for a single nasolabial fold (primary treatment area)	2-point improvement for both nasolabial folds
Subject wrinkle assessment scale	Visual Analog Scale (VAS), assessing wrinkle severity from 0 (no defect) to 100 (very severe defect)	5-point ordinal scale, assessing subject satisfaction with wrinkles on lower part of face
Follow-up time for primary efficacy assessment	Six months after the first injection	Six months after the third injection
Interval between treatments	Two weeks	Five weeks

A total of 123 subjects were randomized in study IT-R-003A, and 115 subjects were randomized in study IT-R-003B. In study IT-R-003A, 79% of the subjects randomized to receive Isolagen Therapy™ actually received at least one treatment, compared to 95% of placebo-randomized subjects (Table 26). In study IT-R-003B, 90% of the Isolagen Therapy™-randomized subjects and 95% of the placebo-randomized subjects received at least one treatment (Table 26).

Table 26. Efficacy Analysis Populations in Studies IT-R-003A and IT-R-003B

	IT-R-003A		IT-R-003B	
	Isolagen Therapy™	**Placebo**	**Isolagen Therapy™**	**Placebo**
Enrolled Subjects, N (ITT population)	61	62	58	57
Treated Subjects, N (%) (ITT population)	48 (79%)	59 (95%)	52 (90%)	54 (95%)

For the Subject assessment of the primary nasolabial fold six months after the initiation of treatment, a greater improvement in mean VAS scores was observed in the Isolagen Therapy™-randomized group compared to the placebo-randomized group by a

statistically significant margin in both studies (Table 27). For the co-primary endpoint based on the blinded Investigator assessment, a statistically significant difference in the Isolagen Therapy™- and placebo-randomized groups was observed in only one of the two studies. For study IT-R-003B, there were 28 subjects (48.3%) in the Isolagen Therapy™ group and 15 (26.3%) in the placebo group who were responders in the Investigator assessment of the primary nasolabial fold at Month 6 (p=0.0079; Table 27). For study IT-R-003A, the percentage of responders for the Investigator assessment was higher in the Isolagen Therapy™ group (21.3%) than in the placebo group (14.5%), but the difference between treatment groups was not statistically significant (p=0.3449; Table 27). Post-hoc efficacy analysis of the MITT Population, which was comprised only of the subjects that actually received treatment, trended toward statistical significance with a p-value of 0.1803 (data not shown).

Table 27. Co-Primary Efficacy Results for the ITT Population in Studies IT-R-003A and IT-R-003B

	IT-R-003A		IT-R-003B	
	Isolagen Therapy™	**Placebo**	**Isolagen Therapy™**	**Placebo**
Subject Wrinkle Assessment				
Mean change in VAS scores	-22.28	-6.21	-24.78	-6.95
p-value[a]	0.0252		0.0166	
Investigator Wrinkle Assessment[b]				
Number of ITT Subjects	61	62	58	57
Number of Responders	13	9	28	15
Percent Responders	21.3%	14.5%	48.3%	26.3%
p-value[c]	0.3449		0.0079	

[a] Analysis of Covariance (ANCOVA) of percent change in VAS from baseline, with Investigator and baseline VAS as covariates
[b] Percentage of responders with 2-point improvement on 6-point ordinal scale
[c] Cochran-Mantel-Haenszel test, stratified by center

5.5. EFFICACY SUMMARY AND CLINICAL SIGNIFICANCE

The pivotal Phase III studies, IT-R-005 and IT-R-006, have demonstrated that Isolagen Therapy™ is efficacious in the treatment of moderate to severe nasolabial fold wrinkles in adults. In two identical pivotal trials, by two co-primary measures of efficacy, a greater proportion of Isolagen Therapy™-randomized subjects responded to treatment of their nasolabial fold wrinkles than did placebo-randomized subjects by a statistically significant margin (Table 9).

Although the primary analysis of efficacy was based on the ITT population, which included all enrolled subjects, a more clinically meaningful comparison of the relative efficacy of Isolagen Therapy™ compared to placebo is provided by analysis of the MITT population, which excludes those subjects who terminated from the study before receiving any treatment. In the MITT population, the proportion of subjects who responded to treatment was higher in both the Isolagen Therapy™ and placebo treatment groups for both efficacy assessments in each of the two pivotal studies. The increase in the placebo response rate, when untreated subjects are excluded from the analysis, reflects the genuine biological response to placebo injection that has been previously described by Isolagen and others (Lu, 2008; Aust, 2008). Nevertheless, the difference in response rate was again higher for the Isolagen Therapy™-treated group compared to the placebo-treated group by a statistically significant margin in both studies (Table 10, Table 11, Table 12).

The stringent criteria applied to the definition of a positive response to treatment were developed in coordination with the FDA and were selected to provide greater statistical validity to the outcome of the pivotal studies. According to the study protocols, only those subjects who achieved a 2-point improvement on the Subject Wrinkle Assessment Scale or the Evaluator Wrinkle Assessment Scale were considered "responders" to treatment. In addition, to be considered a responder based on the Evaluator Wrinkle Assessment, a 2-point improvement was required for *both* nasolabial folds.

Due to the stringency of the protocol-defined response criteria for the pivotal clinical studies of Isolagen Therapy™, the reported percentage of responders in both treatment groups was lower than it would have been had response been based upon a 1-point improvement on either assessment scale. Indeed, many subjects who did not meet the 2-point improvement required to be a responder in these clinical trials, nevertheless experienced an improvement of one point in their Evaluator wrinkle assessment and/or their subject wrinkle assessment (Table 13 and Table 14). For many patients, a 1-point improvement in their satisfaction with their wrinkle appearance represents a clinically meaningful outcome.

The primary efficacy analysis compared the "live" assessments made by the subject and the Evaluator at the last clinic visit (six months following the last treatment administration) to the assessments made approximately 8 ½ months earlier at Baseline. Due to the gradual onset of Isolagen Therapy™ effect, there may be some tendency in the primary efficacy analysis to underestimate the full extent of wrinkle correction achieved by treatment. When the subject and the Evaluator were requested to compare a photograph of the subject taken at six months after the last treatment (Visit 6) to a photograph taken at Baseline, a higher proportion of subjects rated their wrinkle appearance to be "better" or "much better" at Visit 6 than were considered to be responders by the protocol-defined criteria (compare Table 11, Visit 6 results to Table 16). Similarly, a much higher proportion of subjects were considered by the Evaluators to have shown improvement in the severity of the left and right nasolabial folds at Visit 6

than were rated as responders by the criteria of the clinical trial (compare Table 12, Visit 6 results to Table 17). These results demonstrate the stringency of the assessment scales and protocol-defined criteria to evaluate the response to treatment and further suggest that the primary efficacy assessments in the pivotal clinical trials may have underestimated responses that are clinically meaningful.

The time to onset of a sustained response, defined as a 2-point improvement on the Evaluator or Subject Wrinkle Assessment Scales, varied considerably among subjects. Based on the subject assessment, nearly one-half of all subjects who responded over the course of the studies had achieved a sustained response to treatment after only two doses (Visit 3), and approximately two-thirds of subjects had responded by two months after the third treatment (Visit 4; see Figure 6). The Evaluator assessment suggested a somewhat slower response to treatment, with approximately one-third of subjects responding after two doses of therapy, and the proportion of responders rising steadily thereafter to the final study visit (Figure 6). It should be noted that a significant proportion of responders did not respond to therapy by the protocol-defined criteria until the final clinic visit for both efficacy assessments. This is consistent with the biological mechanism of action of Isolagen Therapy™, which is believed to require new deposition of extracellular matrix and/or remodeling of the existing microstructure of the skin to achieve its effect. Because the pivotal studies did not continue wrinkle assessments beyond the six month follow-up visit, it is unknown how many additional responses to treatment may have been observed at later time points.

Similar to the overall response to Isolagen Therapy™, the duration of Isolagen Therapy™ effect cannot be evaluated from the clinical data currently available because the period of follow-up in the pivotal efficacy trials was insufficient. For the subjects with the longest period of follow-up during the study, i.e., subjects who achieved a response after two treatments and were followed for 6 months thereafter, 71% who responded based on the subject assessment, and 61% who responded based on the Evaluator assessment, maintained their responses through at least 6 months (Table 18). The full duration of response for these subjects and for other subjects who responded over the course of the study is unknown. Isolagen plans to collect additional data pertaining to the duration of response to Isolagen Therapy™ in the post-marketing period.

The population of subjects enrolled in the pivotal clinical studies mirrored the population that has typically sought corrective treatments for facial contour deformities, i.e., patients who are White, female and less than 65 years of age. Therefore, there are limited data to evaluate the relative efficacy of Isolagen Therapy™ in subpopulations with other characteristics, such as differences in race or ethnicity, gender or age. The data available to date have not shown a statistically significant difference between the efficacy of Isolagen Therapy™ in White vs. non-White subjects, males versus females, or in subjects greater than or less than 65 years of age (see Table 20 through Table 22).

Because Isolagen Therapy™ is a biological therapy, requiring the handling of living autologous cells, there are several factors that could influence the probability of achieving wrinkle correction satisfactory to the patient. These factors may include the unique characteristics of the patient's own fibroblasts, sensitivity of the product to the conditions of storage and handling, injection technique, or other factors. Nevertheless, in Isolagen's pivotal clinical trials, a higher proportion of subjects with improvement on a variety of wrinkle assessment scales was consistently observed in the Isolagen Therapy™-treated population compared to the placebo treatment group, by a statistically significant margin. Similar results were obtained in earlier, supportive clinical studies. The clinical evaluation of Isolagen Therapy™ has demonstrated that intradermally-administered autologous fibroblasts are effective in the treatment of moderate to severe nasolabial fold wrinkles in adults, both by the stringent criteria of the pivotal clinical trial design and by different, but clinically meaningful measures of improvement in subject satisfaction with their wrinkle appearance.

6. SAFETY OF ISOLAGEN THERAPY™

6.1. INTEGRATED SUMMARY OF SAFETY FROM CONTROLLED CLINICAL TRIALS

6.1.1. Overall Extent of Exposure

All subjects who were enrolled and received at least one administration of study treatment in clinical studies IT-R-001, IT-R-002, IT-R-003A and IT-R-003B, IT-R-005, IT-R-006 and IT-R-007 were included in the safety analysis. Study treatment was defined as Isolagen Therapy™ or placebo administered during open label or randomized, double-blind clinical trials.

The Integrated Safety Population was comprised of 821 total subjects, where 467 subjects received Isolagen Therapy™ and 354 subjects received placebo for their initial course of treatment (Table 28). In Studies IT-R-001 and IT-R-002, subjects that were treated with placebo or the lowest dose (0.5×10^7 cells/mL) of Isolagen Therapy™, and who completed the acute phase of the study (through four months after the first treatment administration), were given the opportunity to receive a second course of three treatments with 2.0×10^7 cells/mL Isolagen Therapy™. A total of 41 subjects who had been previously treated with placebo and nine that had been treated with a low dose of Isolagen Therapy™ opted to crossover to subsequent treatment with Isolagen Therapy™. These 50 subjects are represented in the "Isolagen Therapy™ After Crossover" column of Table 28. However, in subsequent tables the 41 subjects that were initially treated with placebo and subsequently treated with Isolagen Therapy™, appear once in each column in which they were treated. Thus, the total number of subjects who received treatment with placebo was 354 and the total number of subjects who received treatment with Isolagen Therapy™ (as initial treatment or subsequent treatment) was 508.

The extent of exposure to Isolagen Therapy™ or placebo for the Integrated Safety Population is presented in Table 28 for the 821 subjects treated with Isolagen Therapy™ or placebo for their first course of treatment and, separately, for the 50 subjects treated with Isolagen Therapy™ after crossover from a prior treatment. For the purposes of this table, the Number of Injections per Subject refers to the number of areas treated per visit (each corresponding to one "injection") multiplied by the number of treatment visits.

Isolagen Therapy™-treated subjects received an average of 9.1 total injections (range 2 to 20) while placebo-treated subjects received an average of 8.2 injections (range 2 to 15). The number of injections received by Isolagen Therapy™-treated subjects was statistically significantly higher than the average number received by placebo-treated subjects with a p-value of 0.0005 (Table 28). This was due to a few Isolagen Therapy™-treated subjects in Study IT-R-002 that received 17 to 20 injections and subjects in Study IT-R-007 who received 16 injections with no placebo counterpart.

The safety population includes subjects from studies that permitted treatment to a variety of areas on the face. In studies IT-R-001, IT-R-002, and IT-R-007, treatment was permitted to the nasolabial and melolabial folds, perioral lines, glabellar lines, acne scars, and forehead; in studies IT-R-003A and IT-R-003B, only the nasolabial folds and glabellar lines were treated; and in the pivotal studies, IT-R-005 and IT-R-006, treatments were administered to the nasolabial folds only. The average dose per visit varied among subjects based on the total area identified for treatment. Similarly, the total dose per subject varied both as a function of the size of the treatment area and the number of treatment administrations received (up to a maximum of three). The average total dose per subject and the average dose per visit were modestly higher for Isolagen Therapy™-treated subjects (3.7 mL and 1.5 mL, respectively) than for placebo-treated subjects (2.9 mL and 1.0 mL, respectively) (Table 28). This was due to the higher allowed dose per visit (up to 6.0 mL) in Study IT-R-007, in which there was no placebo arm.

The average time from first to last treatment was not different between the Isolagen Therapy™ and placebo treatment groups (Table 28). Among subjects who received < 12 injections, the average time from first to last treatment was 1.8 months for Isolagen Therapy™-treated subjects and 1.9 months for placebo-treated subjects. For subjects with ≥ 12 injections , the average time from first to last treatment was 0.8 months for Isolagen Therapy™-treated subjects and 0.7 months for placebo-treated subjects. The majority of subjects with ≥ 12 injections were from studies IT-R-001, IT-R-002, IT-R-003A, or IT-R-003B, in which subjects were to be treated approximately every two weeks. In studies IT-R-003A and IT-R-003B, subjects could be treated as frequently as every seven days.

Table 28. Extent of Exposure for the Integrated Safety Population by Treatment Group

	Treatment		
	Isolagen Therapy™	**Placebo**	**Isolagen Therapy™ (After Crossover)**
Number of Injections per Subject			
N[1]	467	354	50
Mean (SD)	9.1 (3.7)	8.2 (2.9)	10.0 (3.0)
Median	9	6	12
Range (min, max)	2, 20	2, 15	3, 15
p-value[2]	0.0005		
Total Dose per Subject (mL)			
N	467	354	50
Mean (SD)	3.7 (2.7)	2.9 (0.7)	2.9 (0.4)
Median	3.1	3.0	3.0
Range (min, max)	0.7, 12.0	1.0, 6.0	1.0, 3.6
p-value[2]	0.0044		
Average Dose per Visit (mL)			
N	467	354	50
Mean (SD)	1.5 (1.5)	1.0 (0.2)	1.0 (0.1)
Median	1.0	1.0	1.0
Range (min, max)	0.2, 6.0	0.4, 2.0	0.3, 1.2
p-value[3]	<0.0001		
Number of Subject Months on Study			
N	466	354	50
Mean (SD)	8.2 (2.9)	8.3 (3.4)	7.8 (4.9)
Median	8.0	7.9	11.2
Range (min, max)	0,15.2	1.4,20.9	0.5,12.8
p-value[3]	0.6784		

	Treatment		
	Isolagen Therapy™	**Placebo**	**Isolagen Therapy™ (After Crossover)**
Time from First to Last Treatment (Months)			
Subjects with < 12 Injections			
N	279	250	23
Mean (SD)	1.8 (1.4)	1.9 (0.8)	0.6 (0.2)
Median	1.9	2.1	0.5
Range	0, 9.8	0, 9.1	0.4, 1.0
P-value[3]	0.6022		
Subjects with ≥ 12 Injections			
N	187	104	27
Mean (SD)	0.8 (0.3)	0.7 (0.2)	0.6 (0.2)
Median	0.9	0.7	0.6
Range	0.5, 1.7	0.5, 1.9	0.5, 1.4
P-value[3]	0.6239		

1: N = Number of subjects
2: Wilcoxon Rank Sum test.
3: Two-sample t-test.

The subject demographics of the Integrated Safety Population are summarized in Table 29 by treatment group. The majority of subjects in both groups were White females, less than 65 years of age. These characteristics closely mirror those of the population who seek similar marketed cosmetic procedures (American Society for Aesthetic Plastic Surgeons, 2007). As a result, Non-Whites, males and geriatric subjects 65 years and older are under-represented in the Integrated Safety Population. It should also be noted that pediatric subjects were not evaluated in Isolagen's clinical studies as the Isolagen Therapy™ product is not currently indicated for this population.

The Isolagen Therapy™ and placebo treatment groups were very similar in average age, distribution in age categories, race, gender, height and weight categories, and smoking status (Table 29). The average age of subjects was 52.0 years (range 20 to 77 years) in the Isolagen Therapy™ treatment group versus 54.4 years (range 23 to 79 years) in the placebo treatment group. A modestly greater proportion of Isolagen Therapy™-treated subjects compared to placebo-treated subjects were in the lowest age distribution category of ≤ 50 years (40% for Isolagen Therapy™ versus 31% for placebo). The number and percentage of subjects in the oldest demographic group (≥ 65 years) was

similar between treatment groups [43 subjects (9%) for the Isolagen Therapy™ treatment group versus 41 subjects (12%) for the placebo treatment group.]

As stated previously, the majority of subjects in all Isolagen Therapy™ clinical trials were female. In the Integrated Safety Population, only 38 subjects (8%) were male in the Isolagen Therapy™ treatment group while 34 subjects (10%) were male in the placebo treatment group.

Subjects were evenly distributed by race between the Isolagen Therapy™ and placebo treatment groups; however, the great majority of subjects were White (92% in the Isolagen Therapy™ treatment group versus 90% in the placebo treatment group). A small number of Hispanic subjects were enrolled [26 subjects (6%) in the Isolagen Therapy™ treatment group compared to 24 subjects (7%) in the placebo treatment group]. Only 1% or less of the study population in either treatment group identified themselves as Black or African-American, Asian, American Indian or Alaskan Native, or Other.

Table 29. Demographic Characteristics of the Integrated Safety Population by Treatment Group

	Treatment	
	Isolagen Therapy™ (N=467)	**Placebo (N=354)**
Age, years		
Mean (SD)	52.0 (10.1)	54.2 (9.0)
Median	52.0	54.4
Range	20,77	23,79
Age Group		
≤ 50 Years	185 (40%)	111 (31%)
> 50 Years, < 65 Years	239 (51%)	202 (57%)
≥ 65 Years	43 (9%)	41 (12%)
Gender		
Female	429 (92%)	320 (90%)
Male	38 (8%)	34 (10%)
Race		
White	430 (92%)	319 (90%)
Hispanic	26 (6%)	24 (7%)
Black or African-American	3 (1%)	5 (1%)
Asian	6 (1%)	3 (1%)
American Indian or Alaska Native	0	2 (1%)
Native Hawaiian or Other Pacific Islander	0	0
Other	2 (<1%)	1 (<1%)

The majority of subjects in both the Isolagen Therapy™ and placebo treatment groups completed the studies. Fifty subjects (11%) in the Isolagen Therapy™ group and 22 subjects (6%) in the placebo group did not complete their respective studies. The primary reasons for early termination were subject withdrawal and subject lost to follow-up. Only two subjects failed to complete the study in which they were enrolled due to an adverse even (AE). One Isolagen Therapy™-treated subject in study IT-R-005 terminated prior to study completion due to a Treatment Emergent Adverse Event of

moderate injection site pain, and one Isolagen Therapy™-treated subject terminated early from IT-R-006 due to an AE of mild injection site bruising.

6.1.2. Adverse Events

The adverse events integrated for safety analysis are derived solely from controlled clinical trials conducted by Isolagen. The primary analyses for safety are based on treatment-emergent adverse events (TEAEs), defined herein as any adverse medical occurrence that began or worsened on the first day of treatment administration or any day thereafter during the study period. AEs occurring after subject enrollment and biopsy but prior to the first treatment administration were recorded but have not been included in the integrated safety analysis. Although Isolagen Therapy™ was distributed commercially in the U.K. and Australia, and in the U.S. prior to the filing of an IND, there is limited information available pertaining to adverse events occurring at the non-U.S. locations or in the U.S. during this period.

6.1.2.1. Adverse Events by Frequency

Table 30 and Table 31 present those preferred terms in which at least 1% of subjects in the Integrated Safety Population reported experiencing one or more TEAEs by treatment group. If a subject reported more than one TEAE in a System Organ Class and/or Preferred Term the subject is counted once in that System Organ Class and/or Preferred Term. TEAEs reported by the 41 subjects who were initially treated with placebo in IT-R-001 and IT-R-002 before crossing over to treatment with Isolagen Therapy™ were recorded in the placebo treatment group if they occurred prior to the first administration of Isolagen Therapy™, and were recorded in the Isolagen Therapy™ treatment group if they occurred on or after the first day of treatment with Isolagen Therapy™.

The preferred terms in which the most subjects reported one or more TEAEs were in the System Organ Class (SOC), General Disorders and Administration Site Conditions (Table 30). Sixty-seven percent (n=343) of Isolagen Therapy™-treated subjects and 40% (n=144) of placebo-treated subjects reported at least one TEAE in this class. The preferred terms in which subjects most frequently reported one or more TEAE in the Isolagen Therapy™ treatment group versus placebo treatment group, respectively, were injection site erythema (16% versus 9%), injection site bruising (11% versus 14%), and injection site swelling (14% versus 4%). Less commonly, TEAEs were recorded corresponding to injection site pain (6% versus 2%), injection site haemorrhage (3% versus 5%), injection site edema (4% versus 0%), and injection site nodule (4% versus <1%). Overall in the Integrated Safety Population, the frequency of subjects reporting one or more TEAE associated with the injection site was somewhat higher in the Isolagen Therapy™ treatment group than the placebo treatment group.

TEAEs reported by at least 1% of subjects in a SOC other than General Disorders and Administration Site Conditions are presented in Table 31.

In summary, the majority of subjects that reported any TEAE, reported one or more event in the SOC of General Disorders and Administration Site Conditions and these were overwhelmingly injection site-related events. For the most part subjects in the placebo-treated group reported at least one event in any given preferred term as often as did subjects in the Isolagen Therapy™-treated group. The exceptions were injection site erythema, injection site swelling, injection site pain, injection site edema, and injection site nodule, in which Isolagen Therapy™-treated subjects reported one or more instance more often than did placebo-treated subjects.

Table 30. Injection Site-Related Adverse Events Occurring in at Least 1% of Subjects in Either Treatment Group for the Integrated Safety Population

System Organ Class **Preferred Term**	**Isolagen Therapy™, n (%) (N=508)**	**Placebo, n (%) (N=354)**
General Disorders and Administration Site Conditions	343 (67%)	144 (40%)
Injection Site Erythema	81 (16%)	33 (9%)
Injection Site Bruising	54 (11%)	48 (14%)
Injection Site Swelling	69 (14%)	15 (4%)
Injection Site Pain	31 (6%)	6 (2%)
Injection Site Haemorrhage	13 (3%)	16 (5%)
Injection Site Edema	22 (4%)	0
Injection Site Nodule	20 (4%)	3 (<1%)
Injection Site Papules	8 (2%)	3 (<1%)
Injection Site Irritation	6 (1%)	1 (<1%)
Injection Site Dermatitis	5 (1%)	2 (<1%)
Injection Site Pruritus	5 (1%)	3 (<1%)
Injection Site Reaction	5 (1%)	2 (<1%)

Table 31. Other Treatment Emergent Adverse Events Occurring in at Least 1% of Subjects in Either Treatment Group for the Integrated Safety Population

System Organ Class **Preferred Term**	**Isolagen Therapy™, n (%) (N=508)**	**Placebo, n (%) (N=354)**
Infections and Infestations	80(16%)	81 (23%)
Sinusitis	8 (2%)	15 (4%)
Upper Respiratory Tract Infection	17 (3%)	11 (3%)
Nasopharyngitis	12 (2%)	7 (2%)
Influenza	8 (2%)	8 (2%)
Urinary Tract Infection	5 (1%)	4 (1%)
Bronchitis	5 (1%)	4(1%)
Herpes Simplex	3 (<1%)	4 (1%)
Skin and Subcutaneous Tissue Disorders	47 (9%)	26 (7%)
Acne	8 (2%)	1 (<1%)
Dermatitis Contact	4 (<1%)	5 (1%)
Rash	5 (1%)	2 (<1%)
Musculoskeletal and Connective Tissue Disorders	33 (6%)	27 (8%)
Arthralgia	6 (1%)	4 (1%)
Back Pain	5 (1%)	6 (2%)
Injury, Poisoning and Procedural Complications	24 (5%)	31 (9%)
Foot Fracture	2 (<1%)	4 (1%)
Tooth Injury	1 (<1%)	4 (1%)
Nervous System Disorders	24 (5%)	23 (6%)
Headache	15 (3%)	9 (2%)
Respiratory, Thoracic And Mediastinal Disorders	19 (4%)	15 (4%)
Cough	5 (1%)	3 (<1%)
Nasal Congestion	4 (<1%)	4 (1%)
Vascular Disorders	12 (2%)	6 (2%)
Hypertension	8 (2%)	6 (2%)

6.1.2.2. Adverse Event Relatedness as Judged by the Investigator

Generally, common, local injection site reactions were considered possibly, probably or definitely related to study treatment, but adverse events other than local injection site reactions were generally considered unrelated to study treatment. The relatedness of adverse events reported for the Isolagen Therapy™ and placebo treatment groups was similar, though transient, mild to moderate injection site erythema, swelling, edema, and nodules were reported more frequently with Isolagen Therapy™ treatment. Most related events were those that would be expected from injection of any material.

6.1.2.3. Adverse Event Severity

The majority of reported TEAEs were mild or moderate in severity. More Isolagen Therapy™-treated subjects reported at least one severe event than placebo-treated subjects, and more of the severe events reported by Isolagen Therapy™-treated subjects were considered possibly, probably, or definitely related to study treatment than those reported by placebo-treated subjects. Additionally, Isolagen Therapy™-treated subjects more often reported moderate injection site-related events whereas placebo-treated subjects more often reported mild events. These data suggest that the injection of Isolagen Therapy™ is slightly less well-tolerated than the injection of placebo.

Overall, severe adverse events were infrequently reported. Twenty-six Isolagen Therapy™-treated subjects and 14 placebo-treated subjects reported one or more TEAEs that were considered severe. Of these, six events in four subjects were considered possibly, probably, or definitely related to study treatment. One Isolagen Therapy™-treated subject reported experiencing three severe, definitely related events, injection site erythema, injection site pain and injection site swelling, that resulted in the subject's early termination from the study (see Section 6.1.4). Additionally, one Isolagen Therapy™-treated subject reported possibly related, severe injection site swelling and another reported probably related, severe injection site ischemia. One placebo-treated subject reported definitely related, severe injection site bruising.

6.1.3. Serious Adverse Events and Deaths

6.1.3.1. Serious Adverse Events

Twenty nine SAEs were reported in the Integrated Safety Population. All of these events were considered unrelated or unlikely to be related to study treatment and most proceeded from a condition recorded in the subject's medical history.

6.1.3.2. Deaths

Of the 821 subjects in the Integrated Safety Population, two died during the course of the study.

One subject in study IT-R-005, a 57-year-old White female who received three treatments with placebo, suffered a massive myocardial infarction 5.5 months following the third treatment. The event was considered unrelated to study treatment.

Another subject in study IT-R-006, a 77-year-old white female who was biopsied but not treated, died of cardiac arrest prior to receiving treatment.

6.1.4. Early Termination Due to an Adverse Event

Four subjects who were receiving Isolagen Therapy™ discontinued treatment due to an adverse event. All events were local injection site-related events. A brief narrative for each subject follows.

In the IT-R-003B study, a 58-year-old female who received one Isolagen Therapy™ treatment, experienced moderate injection site pain upon administration of the first treatment. The pain resolved on the day of treatment. The subject was terminated from the study due to this event.

In the IT-R-005 study, a 49-year-old female who received Isolagen Therapy™ treatment, experienced what was considered by the Investigator to be moderate injection site pain upon administration of the first treatment. This event resolved in 10 minutes. The subject was terminated from the study due to this event.

A second subject in the IT-R-005 study, a 55-year-old female who received two Isolagen Therapy™ treatments, experienced injection site erythema, injection site swelling and injection site pain which were each considered by the Investigator to be severe. The events resolved in three to four days. The subject discontinued study treatment but completed all follow-up visits.

In the IT-R-006 study, a 55-year-old female who received two Isolagen Therapy™ treatments, experienced severe injection site bruising at the time of the second treatment; this event resolved in 10 days. A similar event was not reported at the first study treatment administration. The subject was terminated from the study due to this event.

6.1.5. Adverse Events of Special Interest

6.1.5.1. Erythema and Swelling

In general, cases of injection site erythema were mild or moderate and resolved within less than one week. Although erythema is an expected adverse event, there were 9 instances of injection site erythema of unexpected duration (lasting for one or more months), all in Isolagen Therapy™-treated subjects. One instance of severe erythema occurring with severe pain and swelling resulted in a subject's early withdrawal from the study (see Section 6.1.4)

Mild injection site swelling is also an expected AE. Most cases of swelling resolved within one week of treatment. There were two instances of severe injection site swelling and four instance of injection site swelling that lasted more than 14 days. Each of these swelling events occurred in an Isolagen Therapy™-treated subject.

6.1.5.2. Bruising

Mild bruising was also a commonly observed AE that occurred in approximately equal proportion between Isolagen Therapy™- and placebo-treated subjects (Table 30). The majority of these adverse events resolved in one week or less, with a small number of cases lasting for two weeks or more.

6.1.5.3. Papules

There were eight instances of injection site papules in Isolagen Therapy™-treated subjects and three in placebo-treated subjects. All were considered mild or moderate in severity. Most instances of papules considered related to study treatment resolved within one week of onset and all resolved within one month.

6.1.5.4. Nodules

Nodules were reported infrequently in patients treated with Isolagen Therapy™ (20 subjects) or placebo (3 subjects). All were assessed as mild or moderate in severity and all resolved, most within one week of event onset. There were four instances of nodules considered related to study treatment that persisted up to 3 months prior to resolution. All were in the Isolagen-Therapy™ treatment group.

6.1.5.5. Injection Site Ischemia

Injection site ischemia was rarely reported (three events across all studies; two events in Isolagen Therapy™-treated subjects, and one in the placebo group). Two of the events were considered mild. One event in an Isolagen Therapy™-treated subject was considered severe. All of the ischemia events resolved in one day or less without sequelae.

6.1.5.6. Basal Cell Carcinoma

There were two reported cases of basal cell carcinoma (BCC) in the Integrated Safety Population. One subject was a 59-year old Hispanic female who received three treatments with Isolagen Therapy™. The BCC was considered mild and unrelated by the investigator, and was resolved following treatment. A second subject in the IT-R-005 study, a 75-year-old female who received three treatments of Isolagen Therapy™, experienced a basal cell carcinoma on her right upper lip approximately 4 ½ months after her third treatment. The Investigator deemed this event moderate and possibly related to study treatment. The subject was given a local anesthetic and a skin biopsy was performed. A Mohs surgery was performed and the event was considered resolved. The subject completed the study.

Basal cell carcinoma is the most common type of skin cancer where 80% of cases occur in subjects over the age of 50 years. Three out of 10 White individuals will develop basal cell carcinoma in their lifetime. Based on this prevalence, it would not be unexpected for 1-2 subjects to develop basal cell carcinoma during the conduct of the pivotal studies.

6.1.5.7. Keratosis

Three cases of seborrheic keratosis were reported and one case of benign keratosis or hyperkeratosis was reported. Three subjects had received placebo treatment and ranged in age from 57 to 67 and one 53-year-old had received Isolagen Therapy™. Three cases of actinic (solar) keratosis were reported: one in a placebo-treated subject who was 52 years of age and two in Isolagen Therapy™-treated subjects who were 55 and 75 years of age. Whereas seborrheic keratosis is a relatively common noncancerous benign skin growth that originates in keratinocytes in the epidermis, an actinic keratosis, which starts in the epidermis and takes years to develop, is considered precancerous. Both Isolagen Therapy™- and placebo-treated subjects developed these adverse events, and all of these events were considered unrelated to Isolagen Therapy™.

6.1.6. Vital signs

Vital signs were collected in all clinical studies contributing to the Integrated Safety Population. Overall, there were no clinically relevant differences in vital signs between Isolagen Therapy™- and placebo-treated subjects at any study visit.

6.1.7. Clinical Laboratory Evaluations

Clinical laboratory evaluations other than urine pregnancy tests were performed in Studies IT-R-001 and IT-R-002 only. The decision to not include laboratory evaluations in later studies was based on the nature of the investigational product and the results of the clinical laboratory evaluations from these earlier studies.

In Studies IT-R-001 and IT-R-002 blood chemistry, hematology, and limited urinalysis were collected. None of the laboratory values were deemed clinically significant and there were no discernable trends in the data.

6.2. LONG-TERM (12 MONTH) SAFETY FOLLOW-UP

Phone interviews were conducted with 350 of the 359 subjects who completed the last clinic visit in studies IT-R-005 and IT-R-006 to follow up on any unresolved adverse events since the time of the last visit 6 months prior, identify any new adverse events in the subject's medical history, and record any cosmetic or medical procedures or changes in subject medication since the last clinic visit. Subjects were specifically queried regarding any new medical problems, including problems in the vicinity of the treatment area. A total of 167 Isolagen Therapy™-treated subjects and 183 placebo-treated subjects completed the 12 month long-term follow-up interview.

New AEs occurring after Visit 6 were not overtly different in type or frequency between treatment groups for either study. No new AEs reported in Study IT-R-005 were local to the injection site and none were considered possibly, probably or definitely related to study treatment. For Study IT-R-006, there were three events local to the treatment area in one placebo-treated subject (redness, dryness and peel) and these events were not able to be directly assessed by the Investigator. No new AEs in Study IT-R-006 were documented as being related to study treatment. Two Isolagen Therapy™-treated subjects and three placebo-treated subjects in Study IT-R-005 and two placebo-treated subjects in Study IT-R-006 reported experiencing Serious Adverse Events (SAEs) since Visit 6. In both studies, all SAEs reported after Visit 6 were considered unrelated to study treatment.

Adverse events ongoing at Visit 6 were also assessed at the 12-month follow-up interview. In Study IT-R-005, three subjects (two from the Isolagen Therapy™-treated group and one from the placebo-treated group) reported ongoing AEs at Visit 6 that were considered possibly or probably related to the study treatment. One of these AEs (mild ridge at the injection site above the right nasolabial fold) was still unresolved upon completion of the 12 month interview. In Study IT-R-006, no subject reported an ongoing AE at Visit 6 that was considered possibly or probably related to the study treatment. The 12-month safety data support the safety profile of Isolagen Therapy™ demonstrated during the active portion of the pivotal clinical trials.

6.3. SAFETY SUMMARY AND CONCLUSIONS

The analyses of the safety results for the Integrated Safety Population show that the most common TEAEs associated with study treatment were injection site erythema and swelling of mild to moderate intensity and of short duration. Less commonly, subjects reported mild to moderate injection site pain or edema, and infrequently, subjects reported injection site nodules, papules or bruising, or erythema or swelling of unexpected duration or severity. Rare instances of injection site ischemia were reported, as well as instances of actinic keratosis and basal cell carcinoma, all of which were treated or resolved. There was one case of injection site hypersensitivity reported for a placebo-treated subject. Systemic adverse events considered related to study treatment were infrequent and not of concern.

Overall, Isolagen Therapy™ appears to be safe for the treatment of moderate to severe nasolabial fold wrinkles. Isolagen will continue to evaluate the acute and long-term safety of Isolagen Therapy™ in the post-marketing setting.

7. BENEFIT/RISK ASSESSMENT

7.1. BENEFITS OF ISOLAGEN THERAPY™

Isolagen Therapy™ is a novel, autologous cell therapy for dermatological aesthetics. This cell therapy product has been investigated for the treatment of nasolabial fold wrinkles and other facial contour deformities in a total of seven clinical studies (IT-R-001, IT-R-002, IT-R-003A, IT-R-003B, IT-R-005, IT-R-006, and IT-R-007). The pivotal efficacy studies, IT-R-005 and IT-R-006, have demonstrated that Isolagen Therapy™ is efficacious for the treatment of moderate to severe nasolabial fold wrinkles in adults when using the stringent criteria of 2 point improvement in both nasolabial folds. When three treatments of Isolagen Therapy™ are administered at 0.1 mL per linear centimeter every five weeks (± one week), the onset of efficacy, as assessed by both the patient and the investigator, can begin as soon as five weeks after the second treatment and persist at least through six months after the third treatment (long term follow-up evaluations of persistence of response beyond this time period are planned).

7.2. KNOWN AND POTENTIAL RISKS OF ISOLAGEN THERAPY™

Based on Isolagen Therapy™'s safety profile as defined by Phase III and earlier clinical studies, the known risks of Isolagen Therapy™ are limited to temporary injection site reactions, typically of mild or moderate severity. A small number of cases of severe injection site reactions did occur; however, all resolved without sequelae. No serious adverse events possibly related to Isolagen Therapy™ were reported Overall, the known risks from treatment with Isolagen Therapy™ are similar to those from other treatments using intradermal injections with a needle. These risks are minimized through specific training of clinicians in the appropriate technique for Isolagen Therapy™ administration and the supply of detailed instructions to the user with the Package Insert.

Potential risks associated with the use of Isolagen Therapy™ include the risk of hypersensitivity reactions in patients with prior sensitization to bovine-derived products or to the antibiotics used in the early stages of cell culture. These patients are not recommended for treatment with Isolagen Therapy™. There is also a potential risk of inadvertent administration of non-autologous cells to a patient due to human error at the manufacturing site or at the clinical site of Isolagen Therapy™ administration. Isolagen has utilized a patient-specific product tracking system from biopsy collection through drug product delivery as described in Section 3.3.4 to mitigate the risk of inter-patient cross-contamination, and there have been no documented cases of such an event in clinical studies of Isolagen Therapy™. Because Isolagen Therapy™ is a live product in injection medium, there is a risk of administration of non-sterile product to patients. This risk is minimized through adherence to stringent aseptic processing controls during product manufacture and the implementation of appropriate monitoring and treatment of the patient should such an event occur.

Theoretical risks that have been postulated for administration of Isolagen Therapy™ are spontaneous overgrowth of cells, fibrotic scarring and tumorigenicity. The clinical data to date, and Isolagen's previous commercial experience with Isolagen Therapy™, do not suggest an increased risk of these events associated with the use of Isolagen Therapy™.

7.3. BENEFIT /RISK ASSESSMENT

For patients seeking the cosmetic reduction of the appearance of nasolabial fold wrinkles, Isolagen's clinical studies have demonstrated that Isolagen Therapy™ is a safe, efficacious option. Current, commercially-available options for the treatment of facial lines, wrinkles, and folds include surgery, neurotoxins, dermal fillers, lasers, non-ablative therapies, microdermabrasion and chemical peels. Compared to these options, Isolagen Therapy™ represents a novel treatment modality, because it is based on a unique, autologous cell therapy approach that is intended to have a gradual onset and longer duration of effect. The clinical evidence presented here demonstrates that Isolagen Therapy™ is a safe and effective treatment with a uniquely natural origin – the patient themselves. Isolagen Therapy™ is not intended to compete with or replace dermal filler products for the correction of lines and wrinkles, but is instead a new category of treatment, complementing the established therapies.

Isolagen Therapy™ is an individualized treatment. Each patient receives injections that are made specifically for them. Consequently, each patient may respond differently to treatment. Nevertheless, when results of patients' response to the therapy are analyzed as a group, the evidence for the efficacy of Isolagen Therapy™ is very strong.

Isolagen expects that Isolagen Therapy™ will be used commercially by a demographic population that is similar to the overall population seeking cosmetic improvements to nasolabial fold wrinkles. ASAPS statistics show that the majority patients who seek treatment with dermal filler and botulinum toxin products (a market anticipated to be the primary users of Isolagen Therapy™) are White, female and ≥40 years of age (ASAPS, 2007). As experience with Isolagen Therapy™ is limited in non-White (50 subjects in 005/006, 25 of whom received Isolagen Therapy™) and geriatric populations (≥65 years of age; 71 subjects in 005/006, 29 of whom received Isolagen Therapy™), the proposed product label states that efficacy in these populations has not been conclusively determined. Isolagen Therapy™ has not been tested in a pediatric population and will be labeled for adult (≥18 years of age) use only.

Isolagen has evaluated the risks of Isolagen Therapy™ throughout product development, as additional clinical data on the product becomes available. Isolagen's safety database from clinical studies consists of 508 subjects who received at least one injection of Isolagen Therapy™. The Isolagen Therapy™ product has consistently displayed a good safety profile, with the predominant adverse events limited to injection site reactions of a transient nature. In addition, Isolagen's previous experience in marketing Isolagen Therapy™ as an unregulated product in the United States lends additional support for the safety and tolerability of the product.

Isolagen Therapy™ presents a unique opportunity for those seeking aesthetic treatment. Patients now have the option to use their own living cells to treat undesirable contour deformities. The clinical evidence presented here demonstrates that Isolagen Therapy™ is a safe and effective treatment for nasolabial fold wrinkles. The demonstrated cosmetic benefits seen by patients outweigh the risk of predominantly injection-site localized side effects seen with Isolagen Therapy™.

8. PHARMACOVIGILANCE AND POST-MARKETING ASSESSMENTS

8.1. OVERVIEW OF PHARMACOVIGILANCE PLAN

Isolagen is committed to gathering post-marketing safety data to identify novel adverse events or safety signals that require further evaluation for Isolagen Therapy™. Isolagen has developed a preliminary Pharmacovigilance Plan (PVP) for Isolagen Therapy™ in accordance with the requirements of ICH E2E Pharmacovigilance Planning Guidance. A detailed summary of the PVP was provided to FDA in the original BLA, and is described briefly in this section.

Isolagen will be responsible for the pharmacovigilance oversight for the commercial Isolagen Therapy™ program. Key elements of the pharmacovigilance plan include physician prescriber training, safety data collection and medical review including signal detection, establishment and maintenance of a commercial safety database, and periodic reporting to regulatory authorities.

Centers of Excellence, will be established to facilitate the proper training of physician prescribers, as described in Section 3.3. These centers will consist of Isolagen-trained staff that specializes in facial aesthetic treatments. All training (to train the Centers and that performed by the Centers to train physicians) will include proper biopsy collection and shipment to Isolagen, proper treatment preparation and injection technique for Isolagen Therapy™ administration, proper logistics training from biopsy to injection tracking to insure administration of the patient specific cells to only the indicated patient, and types and severity of AEs expected with intradermal Isolagen Therapy™ administration and appropriate medical treatment and follow-up. Isolagen will provide Isolagen Therapy™ only to trained practitioners that are specially certified in the Isolagen Therapy™ Program, and all certified prescribers will be provided access to an Isolagen-sponsored commercial training manual.

The following types of data will be collected as elements of this PVP:

- Serious and unexpected AEs from domestic and foreign sources
- Serious and expected AEs from domestic sources
- Nonserious AEs from domestic sources regardless of expectedness

- Reports of allogeneic cell administration of Isolagen Therapy™ (i.e., administration of cells to a patient other than the intended patient for whom the cells were prepared).

- Isolagen Therapy™ utilization data (e.g., patient demographics)
- Reports of pregnancy during the treatment period

These data will be collected by active and passive surveillance, spontaneous reports, literature reviews, and any post-marketing studies such as *in vitro*, animal, Phase IV clinical, and surveillance investigations. A summary report of all AEs that have been collected will be provided to Isolagen management on a quarterly basis or more frequently, if needed. Analysis of all data will be conducted on a semi-annual basis to alert for possible interactions or safety signals. Proposed analyses to be conducted include AEs reported by severity and relatedness, AEs analyzed by population subgroups (e.g., sex, age, race, ethnicity), AEs associated with the inappropriate administration of Isolagen Therapy™, AEs associated with underlying systemic disease or diseases of the skin, and concomitant use of other cosmetic therapies and/or procedures. A Safety Review Committee composed of Isolagen's Medical Officer, Regulatory Representative, and Manufacturing Operations Representative will meet on a routine basis to review safety data and discuss any changes in the risk/benefit assessment of Isolagen Therapy™.

The data collected will be entered into an electronic safety database. The database will be validated, written procedures will be developed, and a quality control audit program will be established. Isolagen will report adverse events to FDA in accordance with 21 CFR 600.80 and relevant guidances.

8.2. EFFICACY AND SAFETY OF ISOLAGEN THERAPY™ IN SUB-POPULATIONS

Isolagen Therapy™ has been investigated under IND in subjects 18 years and older, but with a limited subset of subjects ≥ 65 years of age. Additionally, small numbers of non-White subjects have been evaluated in the clinic. No significant, overall differences in safety or effectiveness were observed in these sub-populations relative to the total population based on the data collected to date.

Isolagen plans to continue to collect data regarding the efficacy and safety of Isolagen Therapy™ in sub-populations in the post-approval setting. As described in Section 8.1 above, Isolagen plans to collect post-marketing data regarding the demographics for subjects using Isolagen Therapy™. Additionally, AEs will be analyzed by population subgroups (e.g., sex, age, race, ethnicity).

8.3. ASSESSMENT OF DURATION OF EFFECT AND USE OF ADDITIONAL INJECTIONS OF ISOLAGEN THERAPY™

Isolagen has not yet gathered enough information to determine the maximum time the effects of Isolagen Therapy™ may last. In the IT-R-005 and -006 studies, the effects lasted at least through the last study visit, six months after the last treatment. To further investigate the durability of Isolagen Therapy™'s effect, Isolagen is considering an observational clinical study to determine if Isolagen Therapy™-treated participants in the IT-R-005/006 study are still experiencing benefits from their treatment 18-24 months after their last injections. This study would be expected to enroll a subset of the approximately 162 subjects who were treated with three injections of Isolagen Therapy™ for moderate to severe bilateral nasolabial folds in Phase 3 study IT-R-005 or IT-R-006 and who have completed the 12 month safety assessment. No treatment will be administered in this study. The effect of Isolagen Therapy™ at the timepoint of this study would be evaluated by the subject live assessment of the appearance of wrinkles on the lower part of the face, using a 5-point wrinkle assessment scale, and the investigator live assessment of bilateral nasolabial fold wrinkle severity at rest, using a 6-point ordinal scale and photoguide.

Isolagen has not conducted studies of more than three injections of Isolagen Therapy™. In order to investigate the safety and efficacy of additional injections, which may be expected to occur in the commercial setting, Isolagen is considering an additional clinical study. This study would be expected to enroll approximately 40 subjects who were treated with three injections of Isolagen Therapy™ for moderate to severe bilateral nasolabial folds in Phase 3 study IT-R-005 or IT-R-006, who completed the 12 month safety assessment, and whose biopsies have generated enough material for at least one additional injection. Subjects would be enrolled to receive an additional Isolagen Therapy™ injection 12-24 months from the time of their last treatment in study IT-R-005 or IT-R-006. This study would include one follow-up visit 60 days from the additional injection. Safety will be evaluated for all treated patients, based upon the incidence of adverse events. The efficacy endpoints will include the subject live assessment of the appearance of wrinkles of the lower part of the face, using a 5-point wrinkle assessment scale, and the investigator live assessment of bilateral nasolabial fold wrinkle severity at rest, using a 6-point ordinal scale and photoguide.

9. CLOSING STATEMENT

Two pivotal and five supporting clinical studies support the safety and efficacy of Isolagen Therapy™ for the treatment of nasolabial folds in adults ≥18 years of age. This package provides the details of the efficacy and safety results for Isolagen Therapy™. The sponsor presentation will provide an overview of the efficacy and additional details regarding the safety of Isolagen Therapy™ to date.

10. LIST OF REFERENCES

A list of the references cited in this document is provided below. References marked with an asterisk (*) are provided in hardcopy.

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