

## MEMORANDUM

**DATE:** August 11, 2009

**TO:** The Record

**FROM:** Charles Durfor, Ph.D.

**SUBJECT:** BLA - Isolagen therapy

**Product Summary:** Isolagen therapy (IT) consists of viable autologous fibroblast cells suspended in --b(4)-----  
----- and (b)(4) DMSO. The autologous fibroblasts in IT are derived by *in vitro* culture of a biopsy of the recipients' skin using standard cell culture techniques. At the completion of cell expansion the cells are harvested and formulated to a concentration of  $1-2.7 \times 10^7$  cells/ml. The IT cells are washed to ----b(4)----- components before injection. The product is > 98% fibroblasts and cell viability must be --b(4)-

### **Executive Summary:**

Before providing my response to the specific questions posed to this consult review, two major issues should be discussed, because they impact all of the review considerations:

- The study design involved comparing injections of IT and a vehicle control (i.e., (b)(4) and small amounts of ---b(4)---, FBS and DMSO). This control is not a placebo as defined in Stedman's Medical dictionary (i.e., "an inactive substance used as a control in an experiment or test to determine the effectiveness of a medicinal drug"), because there may be toxicities associated with injection of (b)(4) and trace chemicals alone (e.g., promote bacterial infection and/or dermal inflammation). The impact of this on study design is twofold.
  - First, the true safety profile of IT is not derived from a comparison of IT and the vehicle control. Instead the true safety of IT must be derived from a review of the IT arm alone. The IT / vehicle control comparison identifies the safety issues associated with injections of each IT component. For example, treatment emergent adverse events (TEAE) were observed in (144/354 (40%) subjects in the control arm. Thus, the description of IT safety, i.e., "a similar safety profile to that of placebo" (page 39/44) is not appropriate. Instead such statements should suggest that the incidence of subjects reporting at least one TEAE was 68% for IT and 40% for vehicle control. The true incidence of placebo injections was not studied.
  - Second, the efficacy of IT cannot derived from a comparison of IT and vehicle control. Instead this comparison identifies the contributions of the cell and vehicle components. Thus, in general terms, the control treatment should not

be termed a placebo, the efficacy of IT is probably better than and the safety profile is probably worse than suggested by the comparison of IT and vehicle control outcomes.

- The second issue is the frequency of study visits. Information presented on page 37 of the Clinical Study Report for Protocol Number IT-R-006 suggests that clinical visits 1, 2 and 3 occurred at 5 week intervals. Thus, I could not determine how the sponsor accurately collected information about adverse events with regard to time to onset and duration, when such AERs occurred on the scale of days or hours. Were short term AERs were based on a patients' memory at 5 weeks after the last injection? If so it is difficult to assess the accuracy of the AER summary or compare the safety profiles to dermal filling devices where safety information is recorded in patient diaries for the first 14 days after injection and then at a biweekly visits for a month or so..

This consult review was assigned to address the following questions:

1. *Is the Adverse Events profile related to the product acceptable for the proposed indication? Is the proposed labeling of the adverse events appropriate?*

Given the caveat expressed above, the following comments on product safety seem appropriate:

- Because IT requires repeated injections into the skin, it is possible that subjects may develop an allergic reaction to the product.
  - Does the sponsor have data concerning the development of humoral or cellular immune responses to components of the product (i.e., vehicle and *ex vivo* propagated cells)?
  - Does the sponsor have data concerning the incidence of either systemic or local "allergic reaction type" reactions or clinical symptoms that occurred on a more significant level after the 2 or 3 injections (compared to the first injection)? Given the 5 week treatment interval in Studies 005/006 (compared to other trials), the development of a refined immune response is possible. For example, subject --(b)(6)-- (page 54/71 Section 2.7.4) experienced severe injection site bruising at the 2<sup>nd</sup> injection treatment (but not the first) that resulted in study termination. Were there any other clinical or lab values for this patient to rule out whether this was an allergic reaction?
- The adverse event profile presented in the application reflects physician-judged AEs at a few weeks after treatment. As illustrated in the attached label for a commonly used dermal filler (Restylane), CDRH also believes that information from patient diaries recording "adverse outcomes" (a term broader than adverse events) during the first 2 weeks after injection is important information for

patients and physicians to consider when contemplating treatment for an aesthetic improvement. Are such data available for IT?

- From the information reviewed, the size of the injection needle is not clear. This can impact the degree of AEs at the injection site. (Of note most dermal filler devices are injected with 27-30 gauge needles). Such information should be requested as should the incidence of needle blockage and replacement of needles during the implantation procedure, which can result in increased infection and bruising.
- While the overall incidence of AERs presented in the Integrated AER summary for IT and control are generally similar (Section 2.7.4), the incidence of delayed onset AERs in Table 11 (1 day or greater after injection) and duration of AER in Table 12 are greater for the IT cohort. The sponsor should provide information why the presence of cells in IT resulted in more delayed onset and longer duration AERs than vehicle alone (pages 40-43 and pages 44-52 in Section 2.7.4).
- Table 11 (time to onset page 37/71 Section 2.7.4) presents data for all AERs that were judged possibly, probably or definitely related to study treatment along with those with missing relationship. Similarly Table 12 (duration of AERs) presents data on AERs were judged possibly, probably, or definitely related to study treatment as well as missing relationship. Because a true sense of treatment causality is unknown at the time of injection, such a subset of AERs may not fully reflect the true nature of product safety. These Tables (i.e., Time to Onset and Duration of AE) should be requested for all causality AERs.
- Page 53 / 71 of Section 71 describes 4 IT subjects who experienced significant adverse events and were discontinued from the study. In follow-up, did subjects display: 1) any indications of an immune response against IT or 2) permanent symptoms or aesthetic disfigurement resulting from the IT treatment?
- Page 35/99 (Section 2.7.3) describes the lost to follow up subjects in studies IT-R-005/006. The numbers of IT and control patients leaving the study were similar for: 1) withdrawal of consent, 2) adverse events and 3) withdrawal for other reasons.
  - However, 15/210 IT and 5/211 control patients were terminated at the sponsor's request and 5/210 IT and 2/211 control were terminated for non-compliance. The sponsor should explain the significant difference in their termination of IT vs control subjects. In addition, is it possible that control patient withdrawals reflect displeasure with the vehicle injections?
  - The data presented on page 65/99 (Section 2.7.3) suggest a considerable difference in early termination for subjects in the study IT-R-003A/003B (i.e., 34/119 (29%) IT and 9/119 (8%) for Control). This raises concern about the safety of the product. The major differences were subject

withdrawal 16% IT and 7% Control and lost to follow-up 7% IT and 1% control. The sponsor should describe the reasons why a disparity in early subject termination occurred in these studies.

- Page 33/99 (Section 2.7.3) states that the doses used in IT-R-005 were 0.9 – 4.8 ml IT and 1.0-5.4 ml for control. Page 34/99 (Section 2.7.3) states that the doses used in IT-R-006 were 0.7-5.0 ml IT and 1.2-5.1 ml for control. The sponsor should be requested to present information on the AE profile as a function of dose injected.
  - Page 10/44 identifies the anatomical sites treated in Study IT-R-001 (i.e., nasolabial and melolabial folds, perioral lines and glabellar lines, acne scars and forehead). While the number of subjects treated was small (30) it is important to evaluate the number of AEs observed at each anatomical site for product labeling. In other dermal fillers, differences in skin depth, tension and motion at each anatomical site has resulted in difference AE profiles. Was this also observed with IT? Such information could be important for the product label. One example of such labeling is found in the recently approved Sculptra Aesthetic package insert, i.e.,
    - SCULPTRA Aesthetic should be injected into the deep dermis. Superficial injections may be associated with increased local adverse events such as nodules and papules. Take special care when using SCULPTRA Aesthetic in patients with thin skin. Please refer to PATIENT TREATMENT for injection technique instruction.
    - SCULPTRA Aesthetic injection in the peri-orbital area has not been studied. An increased risk of papules and nodules has been reported in published literature after injections in the periorbital area.
  - The submitted information did not include a product label hence comments on its appropriateness were not possible.
2. *What additional safety information would you require before allowing the BLA to be approved?*
- It is possible that the submitted data do not fully reflect the safety profile of the product. For example, page 29/44 states “duration of inflammation was noted only during the injection process and was not reported as an adverse event.” Because the target population is healthy individuals anticipating improvement in appearance, even small changes in swelling, redness or tenderness may be perceived as significant patient concerns. The sponsor should be requested to provide all available data on injection site reactions. If such data are not available, a method for obtaining such data for product labeling should be considered.

- Page 17/44 of Section 2.5 states that 90% of the subjects enrolled in Study 005/006 were female and 88% were white. Data from persons of color is important for premarket approval of this product, because:
  - a. Page 28/44 states – non-white IT-treated subjects had a noticeably higher response rate than white subjects (41% vs 23%, respectively- evaluator assessment). Is this caused by differences in cell response or some other factor? A complementary analysis would be the incidence of AERs as a function of skin type.
  - b. As suggested during the 11/18/08- General and Plastic Surgery Devices Advisory Panel meeting, persons of color do take advantage of dermal filler products.
  - c. As a new technology one should evaluate both *in vitro* and clinical ramifications of IT treatments for cells obtained from different skin types.
  - d. The March 26, 2004 letter to the FDA Commissioner from members of the Congressional Black Caucus expressed the following concerns:

“It is my understanding that an Advisory Committee of the CDRH reviewed a PMA for Artecoll, a permanent cosmetic treatment for scars and wrinkles in the face concerns were raised on Feb 28, 2003. The product had been studied on a sample of 115 men and women but included only one Asian American and no African Americans. The FDA reviewers did not raise any concerns about the lack of diversity in the clinical trials. This is of particular concern because this product could potentially cause disfigurement among African Americans and Asian Americans because of racial differences in scarring.”

“A recent report of the Institute of Medicine (IOM), The Unequal Burden of Cancer, noted “From a scientific perspective...it is critical to include diverse populations in clinical trials to ensure that research findings are generalizable to the entire population. [There are] dangers involved when scientist and public health officials attempt to generalize research findings from relatively homogeneous study populations to broad , more diverse populations.”

“It is important that as Commissioner you should ensure that all medical products reviewed by the FDA include a substantial number of minority patients before even being considered for FDA approval.”

Given the novel nature of IT, I expect the same concerns would be expressed again. Therefore I suggest that the sponsor be requested to re-review all available data (pre and post-market) to determine what information is available on patients with Fitzpatrick Skin types V and VI. Should such data not be available, performance of a separate (open-label) study to collect such information premarket should be considered. Initiation of such a study would of course require prior completion of *in vitro* analyses of sufficient fibroblast cultures from persons of color to demonstrate that the cellular characteristics of expanded cells from persons with Fitzpatrick skin types V and VI behave in a similar manner to previously characterized cells. The one reason to not pursue this approach would be the belief that the risk of hypertrophic scarring and keloid formation resulting from the initial biopsy procedure presents an unreasonable risk to the subject.

- Related to the issues associated with person of color, page 38/99 provides the baseline demographics for subjects in Study IT-R-005/006. While the sponsor identifies the ethnicity of the patient population, it does not describe the Fitzpatrick Skin type of subjects. Because members of any ethnic group may have different skin color or sensitivity to hypertrophic scarring, such data should be requested.
  - Page 14/44 of Section 2.5 suggests that IT is a localized cell therapy. The sponsor should be requested to provide all available data concerning the migration of cells away from the injection site or into the systemic circulatory system. Also to more fully understand the risks of malignancy associated with product use, all available data on the duration of IT cells after implantation should be requested.
  - The integrated summary of safety provided on page 38/44 suggests that some patients have been followed for up to 15 months after treatment. Please provide a summary of delayed or long duration AEs (> 6 months) including type of event, duration, time to onset and medical intervention required to stop the AE.
  - Page 9/44 identifies commercial experience in the UK, but does not clarify how many patients were treated or the safety profile associated with these subjects. The reason why was the product withdrawn from the market is provided. However, contact with the UK regulatory authorities (through the FDA International Affairs staff) could provide important information on the UK's regulatory authority's perspective of product safety.
  - Page 8/44 (Section 2.5) stated – US Commercial experience included approximately 100 clinicians in the fields of dermatology, facial plastic surgery, and reconstructive plastic surgery, who treated patients with facial rhytids, scars, hypoplastic lips, burns and other problems. There was a reported patient experience of almost 1,000 patients, 354 of whom were included in the efficacy population of an informational retrospective report (Section 5.3.5.4). All available data on the safety of the product should be obtained for FDA review.
3. *What post-marketing safety monitoring plan would you require, given the available population demographic data (age, gender, and ethnicity) as well as possible concerns regarding long-term safety?*

No comment at this time.

4. *Please comment on provision of relevant product label information about biopsy failure (requesting information from the sponsor) and fibroblast manufacture failure (about 4.3%).*

The submitted information did not include a product label hence comments on its appropriateness were not possible.

5. *Please comment on the primary/secondary endpoints and data validation.*

As discussed below, the sponsor had two primary endpoints one which was not validated (the subject assessment) and the second which was a validated measure of wrinkle severity (i.e., the Lemperle Wrinkle Severity Scale). Because the sponsor did not provide information concerning the degree or success of training blinded investigators in using this Measure, it is difficult to evaluate whether product efficacy was demonstrated. For example, while the scale has been validated so that a 1 point change is believed to be clinically significant a very high number of control subjects (30%) improved by 1 grade at 6 months. Whether this reflects the efficacy of the vehicle control or poor application of the Lemperle Scale by blinded investigators is unknown.

*In-depth comments include:*

- Page 18/44 Section 2.5 describes the primary efficacy endpoints for Studies 005/006 as:
  - **Subject wrinkle assessment** – a live comprehensive assessment of wrinkles of the lower part of the face at visit 6 using a 5 point scale where response was defined as a 2 point or better improvement
  - **Evaluator wrinkle severity assessment** – a blinded evaluator performed a live assessment of bilateral nasolabial fold wrinkles at rest at visit 6 using a 6 point ordinal wrinkle severity scale with a photo guide (Lemperle, 2001). Response was defined as a 2 point or better improvement compared to baseline.
    - a. Regarding the subject wrinkle assessment, to my knowledge, the global assessment scale published by Cohen and Holmes has not been validated as a meaningful predictor of clinical appearance. The following questions and comments on this point are:
      - i. In general, subject data have not been employed as a primary endpoint in device trials because it is difficult to determine whether adequate training of patients has been achieved. Such subjects are particularly prone to the “halo effect” in which subjects judge a return to a “baseline” appearance (after resolution of the swelling, redness and tenderness associated with implantation) to be a significant improvement. This may explain why 30% of the control subjects in IT-R-005 and 18% of the control subjects in IT-R-006 judged themselves as treatment successes.
      - ii. Any scale that judges patient improvement relies on either subject memory or comparison of live and photographic assessments. Both approaches may have significant flaws.
    - b. Regarding the blinded evaluator wrinkle assessment.

- i. While this reviewer agrees that the Lemperle scale is both validated and the basis for approval of several medical devices, each approval not only required the use of the validated scale, but also evidence that the blinded evaluators had been adequately trained to use such a scale. Such evidence is generally provided in the form of inter and intra –rater reliability values demonstrating a high level of agreement between raters and for a single rater at a 2 week or greater interval. Such information is also important because page 10/44 (Section 2.5) states that “the reasons for the missed endpoint in 003A (investigator assessment) are believed to have included insufficient investigator training and sub-optimal dosing.” Thus, the sponsor should submit data illustrating improved investigator training to support their hypothesis of product effectiveness.
  - ii. Such data would also assist in determining whether the high incidence of complete responders in the vehicle control-group reflect an ability of the blinded evaluators to assess patient appearance accurately or improved wrinkle severity caused by the inflammatory responses associated with vehicle injections. For example, in Study IT-R-005/006 page 32/44 (Section 2.5) 30% of the control subjects achieved a 1 grade or greater response at 6 months after treatment (Evaluator assessment).
  - iii. While a one point improvement on the Lemperle scale was not considered the primary study endpoint, the scale is validated such that a one point difference is clinically significant. Thus, if the sponsor can provide data documenting the adequate training of evaluators and explain why high incidence of control subjects were responders, review of the 1 point data will be important.
- Page 20/44 (Section 2.5) states that in Study IT-R-005 Blinded Evaluators (the most objective form of judging product performance) rated 33/100 (33%) of IT and 7/103 (7%) of control subjects as responders. In Study IT-R-006, Blinded Evaluators rated 21/110 (19%) of IT and 8/108 (7%) of control subjects as responders (as judged by a 2 grade improvement).
  - i. The sponsor should explain why a 14% difference in IT responders’ rates was observed for the studies 005/006 and why they believe the results of the two studies may be combined into a unified description of product performance.
  - ii. The sponsor should explain why a 14% difference in responder rates between studies 005/006 is clinically not significant (so that the results of Studies may be pooled), but a 12% difference between treatment and



control in Study IT-R-006 (i.e., 19% vs. 7%) should be considered clinically not significant.

- iii. The overall success rate for IT patients in Studies IT-R-005/006 was 54/210 (25.7%) rate. While the study is statistically significant, should a failure rate of greater than 74% to achieve a 2 or greater improvement in wrinkle severity be considered clinical benefit?

6. *The assessments used for evaluation of the secondary efficacy endpoint are based on comparing photographs taken at baseline and at pre-specified post-treatment time points. The sponsor has not submitted any photographs in the BLA package. Please comment on the relevance of real photographic data to safety and efficacy reviewing purposes.*

No comment at this time.

7. *Do you have any additional comments about safety, efficiency, labeling and post-market issues?*

- Page 11/44 of Section 2.5 states that the 12 month data for Study IT-R-007 – Phase 2 Study that used up to a 3 times higher IT dose will be “provided in a safety update during the BLA review period.” When will such data be submitted for review?
- The Integrated patient population data presented on page 40/99 (Section 2.7.3) suggests that 100% of the IT population was over 40 years old. Thus, the sponsor’s proposal for an indication for product use including subjects over 18 years old is not appropriate.
- Page 7-44 (section 2.5) states – that IT is “thought to increase the synthesis of extracellular matrix components, including collagen reducing the severity of these wrinkles. Page 24/27 (Section 2.3.P) states that a collagen production assay will be evaluated as a potential Potency assay for IT. Because the predictive nature of the collagen production assay for clinical benefit is unknown and because a Phase 3 study is the appropriate place to validate the clinical predictive nature of such a Potency assay, the sponsor should be requested to provide the following data comparing:
  - 1) increases in patient skin thickness and aesthetic outcome; and
  - 2) increases in patient skin thickness and *in vitro* production of collagen.

For example, approval of Sculptra P030050 in HIV subjects was partially based on data collected on increases in skin thickness by ultrasonography in the cheek area at Baseline, Weeks 8, 24, 48, 72 and 96.

- Page 35/99 (Section 2.7.3) states that 13 IT and 5 control subjects were withdrawn because the product could not be manufactured within the required time frame. Regarding this observation,
  - The sponsor should explain why control product could not be readily manufactured.
  - The sponsor should be request to identify any potential predictive factors for when a subject's cells may not be successfully cultured for IT manufacture.
- The data for Studies 005/006 suggest that only 25% of the subjects were responders (i.e., 2 or greater improvement in wrinkle severity). Comparing this to the unknown risks of receiving injections of *in vitro* expanded cells and the reported rate of TEAE 343/467 (68%) subjects raises significant questions in the risk/benefit ratio for IT use.
- Concerning poolability of data, the blinded evaluator at one site (Site 6100) in the IT-R-006 study had more control subjects improving (2/17-12%) compared to IT subjects (1/19 (5%). While the number of subjects at each site is small, the sponsor should clarify why this trend against the product was observed.
- Vascular occlusion, infarction, tissue necrosis and embolic phenomena have been reported during implantation of device dermal fillers implantation into blood vessels. Were such events observed in premarket/post market studies with IT?

#### **Review:**

The following clinical data were presented in this application and summarized on page 35-36/44 Section 2.5)

- **Study IT-R-001** – was a Phase 2 study (2 centers) that was a double-blind, randomized, placebo controlled trial for treatment of nasolabial and melolabial folds, perioral lines and glabellar lines, acne scars and forehead. 30 IT and 10 placebo subjects were treated.
- **Study IT-R-002** – Phase 3 Study (10 centers) double-blind, randomized, placebo-controlled study for treatment of facial contour deformities and scars. 151 subjects were treated with either IT (n=112) or placebo (n=39).
- **Study IT-R-003A/3B** were Phase 3 Studies (3 centers) that were double blind, randomized and placebo-controlled trials for treatment of contour deformities (specifically nasolabial fold wrinkles and glabellar lines. Subjects received 3 IT treatments ( $2 \times 10^7$  cells/ml) or placebo once every 14 days. A total of 100 IT and 113 placebo controlled subjects were enrolled in each study.

While both primary endpoints were achieved in study IT-R-003B, the failure to meet the investigator assessment primary endpoint in study IT-R-003A lead the sponsor to propose an additional Phase 3 study.

- **Study IT-R-005/6** – Phase 3 Studies (005- 7 centers & 006 – 6 centers) were double-blind randomized vehicle (aka placebo) controlled studies In the treatment of nasolabial folds wrinkles. Subjects received 3 treatments of  $1-2 \times 10^7$  cells/ml of IT or vehicle control at 5 week intervals. In study IT-R-005 there were 83 IT and 92 placebo subjects. In study IT-R-006 there were 98 IT and 99 placebo subjects. Thus, for the total IT-R-005/6 study tere were 181 IT and 191 vehicle (placebo) controlled subjects. The outcomes from these studies form the dataset for product effectiveness.

**The primary endpoints were:**

- **Subject wrinkle assessment** – a live comprehensive assessment of wrinkles of the lower part of the face at visit 6 using a 5 point scale where response was defined as a 2 point or better improvement. This scale (page 20/99 Section 2.7.3) relates to subject satisfaction.
- **Evaluator wrinkle severity assessment** – a blinded evaluator performed a live assessment of bilateral nasolabial fold wrinkles at rest at visit 6 using a 6 point ordinal wrinkle severity scale with a photo guide (Lemperle, 2001). Response was defined as a 2 point or better improvement compared to baseline.

**Efficacy results**

- In Study IT-R-005 Blinded Evaluators (the most objective form of product performance) rated 33/100 (33%) of IT and 7/103 (7%) of control subjects as responders. In Study IT-R-006 Blinded Evaluators rated 21/110 (19%) of IT and 8/108 (7%) of control subjects as responders.
- In Study IT-R-005/006 page 32/44 (Section 2.5) suggests that 60% of the IT and 30% of the control subjects achieved a 1 grade or greater response at 6 months after treatment (Evaluator assessment).
- Regarding patients achieving a 1 point or greater response by the blinded evaluator (page 57/99 (Section 2.7.3) the Integrated summary for Study IT-R-005/006 revealed 116/210 (55%) IT and 68/211 (32%) for control.
- Duration of effectiveness as judged by the blinded evaluator is presented on page 92/99 of Section 2.7.3. This presentation omits all subjects who did not achieve a 2 point or greater improvement. More than 85% have a long lasting response (> 200 days).
- Safety in IT-R-005
  - 29 (35%) IT and 27 (29%) control patients reported at least 1 possible, probably or definitely related TEAE. 3 severe events were reports were reported in a single patient.
  - 7 SAEs were reported by 5 subjects. This includes 1 study death in the control arm.
- The subjects enrolled were largely grade 3 (moderate deep) and grade 4 (deep wrinkle). ~ 10% had Grade 5 (very deep wrinkles). – page 43/99 (Section 2.7.3)
- **Study IT-R-007** – Phase 2 Study was multi-centered, open-label for IT treatment of facial wrinkles and creases other than nasolabial folds. Each subject received 2 treatments up to 6 ml of  $1-2 \times 10^7$  cells/ml administered once every 5 weeks. 45 subjects were treated. 45 subjects treated.

- **Study IT-A-008** – Acne scars ----- (b)(4)----- efficacy in treatment of acne scars with subjects receiving ---b(4)-----  
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The data from Studies IT-R-005/006 were reviewed for safety and efficacy. The data from all trials were only evaluated for product safety. The data from Study IT-R-003A/B were not reviewed for efficacy because:

- 1) the patient populations were different (i.e., 003A/003B enrolled subjects with 2-5 wrinkle severity vs Studies 005/006 which enrolled subjects with 3-5 wrinkle severity -page 27/44 Section 2.5);
- 2) the dose and timing of IT treatments were different (see page 25/44 Section 2.5);
- 3) Studies 003A/003B evaluated the primary nasolabial fold, whereas Studies 005/006 evaluated both nasolabial folds;
- 4) a different primary subject assessment tool was used (see page 26/44 Section 2.5); and
- 5) the blinded evaluator measure used in 005/006 included more descriptive text for each wrinkle severity point than used in Studies 003A/003B.

This made comparison of data from studies 003A/003B and 005/006 impossible. It should also be noted that because subjects treated for acne scars generally are more pleased with their outcome (and the facial defect has a different anatomical basis), data from acne scars may not be predictive of wrinkle treatment outcomes.

Other clinical data available for safety evaluation.

- IT was commercially available in the US from 12/95 – 2/99. After that an IND was required
- Integrated safety summary – (page 38/44 Section 2.5) included 467 IT and 354 vehicle (control) subjects followed for a mean time of 8 months and a range of ~ 15 months.
  - 343/467 (68%) of IT and 144/354 (40%) of the control subjects reported at least one treatment-emergent adverse event (TEAE).
  - One patient experienced an onset of basal cell carcinoma at 141 days after injection. The investigator judged this event as possibly related to IT. The sponsor disagrees.

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Date