

Review Memo, December 9, 2009 - Laviv

MEMORANDUM

Wilson W. Bryan
Clinical Branch Chief
FDA/CBER/OCTGT/DCEPT/CEB

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| BLA# | 125348/0 |
| Submission date | March 6, 2009 |
| Review date | December 9, 2009 |
| Product Reviewers | J. Terrig Thomas, Ph.D. Donald Fink, Ph.D. |
| Pharm/Tox Reviewer | ATM Shamsul Hoque, Sc.D. |
| Clinical Reviewers | Agnes Lim, M.D. Yao-Yao Zhu, M.D., Ph.D. Changting Haudenschild, M.D. (Team Leader) |
| Clinical Team Leader | Bruce Schneider, M.D. |
| Office Director | Celia M. Witten, Ph.D., M.D. |
| Regulatory Project Manager | Lori Tull, RAC |
| Biostatistician | Shiowjen Lee, Ph.D. |
| Consults | Office of Biostatistics and Epidemiology / Division of Epidemiology (Zinderman, Buckler) Center for Drug Evaluation and Research / Division of Dermatology and Dental Drug Products (Liedtka) Center for Devices and Radiological Health/Office of Device Evaluation / Division of Surgical, Orthopedic and Restorative Devices (Alexander; Durfor) |
| Advisory Committee | Cellular, Tissue, and Gene Therapies Advisory Committee, October 9, 2009 |
| Sponsor | Fibrocell Technologies (formerly Isolagen Technologies) |
| Product | Autologous cultured human fibroblasts (azficel-T; formerly Isolagen Therapy) |
| Proposed Use | Treatment of moderate to severe nasolabial fold wrinkles |
| Recommendation | Complete Response |

Fibrocell Technologies has submitted biologics license application (BLA) 125348/0 for azficel-T for the treatment of moderate to severe nasolabial fold wrinkles.

Efficacy

As discussed in the Clinical Reviews and in the deliberations of the Cellular, Tissue, and Gene Therapies Advisory Committee (AC), the two Phase 3 studies (IT-R-005 and IT-R-006) provide substantial evidence of effectiveness for the proposed indication. There is insufficient data to assess effectiveness beyond six months. The magnitude of the benefit (an improvement in wrinkles) is small.

The BLA does not provide sufficient data to assess effectiveness in males, non-Whites (Fitzpatrick skin types IV through VI), or older (> 65 years) people. These deficiencies should be noted in labeling, and addressed in post-marketing studies (preferably post-marketing requirements).

No additional evidence of effectiveness is necessary prior to BLA approval.

Safety

The safety database consists primarily of approximately five hundred subjects who were exposed to azficel-T during clinical development. However, the BLA also contains less rigorous safety data from commercial experience with the product. This commercial experience includes approximately nine thousand patients who received the product when it was marketed in the United States and United Kingdom.

The BLA does not adequately address several safety issues. Specifically, the BLA does not provide sufficient data to assess safety in non-Whites (Fitzpatrick skin types IV through VI) or older (> 65 years) people. Considering the chronic nature of the proposed indication, there is a reasonable expectation that some patients would be exposed to repeat administration(s) of the approved product. However, the BLA provides no data regarding the safety of repeat courses of administration. In addition, the BLA includes insufficient data to assess long-term (beyond one year) safety. As discussed by the AC and in the Clinical Reviews, specific safety concerns include tumorigenicity, immunogenicity, and cosmetic issues (i.e., scarring and keloid formation).

In determining the appropriate size of the pre-approval safety database, factors to consider include the magnitude of the expected benefit, the duration of exposure, the size of the indicated population (i.e., the availability of subjects), and the nature of the product. For azficel-T, the magnitude of the benefit, a decrease in wrinkles for six months, is small. The indicated population is probably large (millions of people in the United States) and therefore does not restrict drug development. The duration of exposure depends on the duration of cell survival post-administration and has not been studied. The product is a first-in-class fibroblast cell therapy, so there is no reassurance provided by experience with one or more closely related products. As an autologous product, azficel-T may have some inherent safety, relative to a product that is completely new to the patient. The commercial experience safety database is relatively large and therefore provides some reassurance of safety; however, the commercial experience did not include rigorous collection of adverse event data. Considering all of these factors, the size of the azficel-T safety database is insufficient.

Considering both the clinical trial and commercial safety experience, additional evidence of safety is necessary prior to BLA approval. This evidence may come from additional nonclinical studies, post-administration biopsy study to assess histopathology and product survival, and/or additional subject exposure with rigorous monitoring for adverse events.

If azficel-T is approved without a substantial increase in the safety database, a post-approval registry should be required to assess tumorigenicity, long-term safety (particularly immunogenicity), keloid formation in non-Whites, and the safety of repeat courses of administration.

Labeling (adequate directions for use)

Azficel-T would be administered by intradermal injection by health care providers. Training of health care providers may be essential for optimal product safety and efficacy. If this product is approved, the product label should emphasize training of health care providers.

Recommendation Complete Response

Recommended comments for a Complete Response letter

With regard to clinical comments for a Complete Response letter, I agree with the recommendations of the clinical primary review team.

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