Dermatologic and Ophthalmic Drugs Advisory Committee

Questions to the Committee

May 23, 2002

License # STN BL 125036/0 **Alefacept**
Biogen, Inc.

Indication: for the treatment of patients with chronic plaque psoriasis who are candidates for phototherapy or systemic therapy

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I. Safety of Alefacept

A. Lymphocyte reduction and risk of infection

Alefacept treatment causes reductions in total lymphocyte counts and T cell subsets. In study 711 (IV study), approximately half of the participants experienced at least a single occurrence of a CD4 cell count below the lower limit of normal at any time during a treatment course (12-week dosing and 12 week follow-up). In study 712 (IM study), this figure was approximately 30%. In some patients, lymphocyte reductions are long lasting. Twelve weeks following the last dose, approximately 20% of study 711 participants had CD4 counts below normal.

The total experience of patients receiving more than 2 cycles is limited. Approximately 50% (N=756) of total alefacept treated patients received 2 courses of treatment, 15% (N=199) received 3 courses, and 10% (N=140) received 4 or more courses. Available data (based on two cycle of treatment) suggest that lymphocyte reductions may be cumulative in some people.

A central issue is whether lymphocyte reductions result in clinical sequelae. In the phase 3 trials, serious infections were reported in 1/413 (0.2%) of placebo and 8/876 (0.9%) of alefacept treated patients. There was no apparent relationship between lymphopenia and infections, and no opportunistic infections were observed. However, some of the infections among patients on alefacept were associated with a protracted course (e.g. cellulitis→septic shock and multi-organ failure, external otitis→facial cellulitis)

The maximum duration of alefacept treatment was 3 months, with a minimum interval of 3 months prior to subsequent dosing. Normal lymphocyte and CD4+ cell counts were required before the first treatment cycle and normal CD4+ cell counts required for subsequent cycles. If licensed, lymphocyte monitoring and dose adjustments may not be as frequent as was performed in the clinical trials. This raises concerns that depth and duration of lymphopenia may be more pronounced, with unknown clinical consequences.

1) Has the sponsor generated sufficient data pre-marketing to characterize treatment related effects on lymphocyte reductions? Given that the sponsor is proposing the product be indicated for multiple cycles, please comment on the adequacy of the data to support multi-cycle use.

2) Please discuss the optimal way(s) to generate additional data on infectious risks.

B. Changes in antigen response

The effects of alefacept on delayed-type hypersensitivity (DTH) were evaluated in two trials, Study 703 (an uncontrolled dose-escalation study) and 708 (a controlled dose-ranging study). Responses to seven microbial antigens applied to non-lesional skin were evaluated. DTH shifts from + to – were observed for isolated antigens (range 0-3 per patient) in study 703 without relationship to dose. In study 708 the number of DTH shifts from + to – was higher in the alefacept groups compared to placebo. There are no reports of patients treated with alefacept who developed tuberculosis. No studies have been performed to evaluate the ability to mount a response to vaccines.

1) Should all individuals be evaluated for latent tuberculosis infection with a tuberculin skin test prior to therapy with alefacept? If a latent infection is uncovered, please discuss how such individuals should be managed with respect to use of alefacept.

2) Should subject monitoring include periodic assessments of DTH?

3) Should the sponsor perform studies to evaluate the ability to respond to immunizations such as pneumococcal or influenza vaccines?

C. Malignancies

Individuals with severe psoriasis are at higher risk for developing malignancies, particularly skin malignancies (squamous cell carcinoma) and lymphomas. The pathophysiology of the disease and more importantly some of the treatments (PUVA, etc) may predispose to neoplasia. Alefacept is a new biological with known immunosuppressive effects. In the controlled studies, rates of malignancy were: 2/413 (0.5%) for placebo and 10/876 (1.1%) for alefacept treated patients. Most of the malignancies were squamous cell skin cancers though one alefacept treated patient developed B cell lymphoma during an open label extension, and a single occurrence of B cell lymphoma was seen in a non-human primate study.

It is difficult to detect an increase in the rate of malignancies in the absence of larger numbers of patients exposed and longer periods of follow up and in the absence of a concurrent control group.

1) Please discuss how best to evaluate the risk of malignancies. Should all people who receive alefacept enter a registry?

II. Dose

In the phase 2 study, dosing was weight based. Weight did not appear to be an important factor in the pharmacokinetic profile of alefacept. Thus, the phase 3 studies were conducted using fixed doses for both the IV and IM routes of administration, with the exception that very low weight subjects (< 50kg) received a 30% reduction in the dose. In study 711, efficacy responses were approximately 4 fold less in people weighing >85 kg vs ≤85 (5% vs 19%, respectively after adjusting for placebo effect). Similar trends in response were seen in study 712 (IM study), where response rates for people >85 kg and ≤85 kg were 12% vs 19%, respectively after adjusting for

placebo effect. This suggests that heavier study subjects may have been under-dosed; however, such patients appeared to experience a degree of lymphopenia similar to those who were below the weight median.

1) Please discuss the degree to which the dose has been optimized. Should the sponsor conduct further studies of weight-based dosing?

III. Efficacy Outcomes

In the phase 3 studies the primary assessment was the proportion of patients with ≥75% improvement in PASI score from baseline. Patients receiving systemic therapy or phototherapy were considered treatment failures in the primary efficacy analysis. Physician's Global Assessment (PGA) of "clear" or "almost clear" was an important secondary outcome. By PASI assessment, 10-16% (absolute) more alefacept-treated patients responded compared to placebo, and 7-9% (absolute) more alefacept-treated patients responded by PGA assessment.

Of three different instruments used to assess patient reported outcomes, the overall Dermatology Life Quality Index (DLQI) score was considered to be the primary score. The DLQI score ranges from 0 (best) to 30 (worst). The DLQI was measured at baseline and after the end of treatment. The between group difference, which favored alefacept, was no more than 3 points after adjusting for baseline DLQI score.

1) Please discuss the choice of ≥75% improvement in PASI to demonstrate clinical benefit with the PGA of clear or almost clear as the key secondary outcome measure.

2) Do the DLQI data suggest a meaningful benefit over and above that provided in the PASI and PGA outcomes?

IV. Risk/Benefit

1) Has the sponsor shown that alefacept is safe and effective for use in adults with chronic plaque psoriasis who are candidates for phototherapy or systemic therapy?

2) If the answer is yes, then, please comment on the issues regarding the product label, as discussed below.

V. Product Label

The sponsor has proposed that the indicated population be "patients with chronic plaque psoriasis who are candidates for phototherapy or systemic therapy." Eligibility criteria permitted enrollment of individuals who had received prior systemic or phototherapy as well as those who were naïve to such prior therapies.

1) Should the indicated patient population be limited to people who have failed or had an inadequate response to phototherapy or systemic therapy rather then "candidates for" such therapies?

2) Should the indication specify 'moderate to severe' plaque psoriasis?

3) Please discuss the recommendations that should be included in the label regarding lymphocyte monitoring and subsequent dosing. Specifically, should the label state that lymphocyte counts and CD4 counts be followed for all subjects as was performed in the clinical studies?

4) Please comment on the types of information to include in the warnings regarding the risks of infection and malignancy.

5) What, if any, information regarding the DLQI outcomes would be useful to provide in the product label?

VI. Studies in Other Populations

A. Adults with other forms of psoriasis

Individuals with erythrodermic, guttate, palmar, plantar pustular, or generalized pustular psoriasis were excluded from the clinical studies.

1) Should the sponsor evaluate the safety and efficacy of alefacept in people who have other forms of psoriasis?

B. Children

Pediatric patients have not been evaluated in the clinical development program thus far. Federal regulations require sponsors to conduct trials in pediatric populations for a use approved in adults if the product is to be used in large numbers of affected children or it represents a meaningful therapeutic benefit. Trials in children may be deferred to after market approval for adults, particularly if concerns about toxicity warrant the collection of more safety data in adults before children are exposed. Biogen has requested and received a deferral for the conduct of pediatric studies.

1) Should alefacept be studied in pediatric patients with psoriasis? If so, please discuss the timing of such studies relative to accumulation of postmarketing safety data in adults.

2) What are appropriate efficacy outcomes for pediatric studies?

3) How should children be assessed for loss of response to recall antigens or ability to respond to childhood vaccines?

C. People with concomitant HIV infection

HIV infection was an exclusion criterion. HIV is a precipitating factor in psoriasis.

1) Given the effects on lymphocyte depletion, please discuss whether patients with concomitant HIV infection should be studied. If studies are appropriate, please discuss what lymphocyte values should be considered for dosing decisions. If studies are not warranted, what information should be included in the label about use in persons with HIV (and other populations at risk of infections)?