In study 1, patients were randomized to receive one or two courses of AMEVIVE® 7.5 mg administered by IV bolus. The first and second courses of the two-course cohort were separated by at least a 12-week post-dosing interval. A total of 553 patients were randomized into three cohorts (Table 1).

Table 1. Treatment Schedule for Study 1

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>AMEVIVE® (15)</th>
<th>Placebo (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 2</td>
<td>AMEVIVE® (18)</td>
<td>Foscarnet (18)</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>Placebo (18)</td>
<td>AMEVIVE® (18)</td>
</tr>
</tbody>
</table>

Study 2 provided a basis for comparison of patients treated with either 10 mg or 15 mg AMEVIVE® IM. One hundred seventy-three patients were randomized to receive 10 mg of AMEVIVE® IM, 166 to receive 15 mg of AMEVIVE® IM, and 168 to receive placebo.

In Studies 1 and 2, 77% of patients had previously received systemic therapy and/or phototherapy for psoriasis. Of these patients (PASI) at least 75% from baseline at two weeks following the 12-week treatment period. Other treatment responses included the proportion of patients who achieved a score of “almost clear” or “clear” by Physician Global Assessment (PGA) and the proportion of patients with a reduction in PASI of at least 50% from baseline at 12 weeks post dosing through study day 56.

Table 2 shows the treatment response in the first study of Cohort 1 and Study 2. Response to treatment in both studies was defined as the proportion of patients with a reduction in score on the Psoriasis Area and Severity Index (PSA) of at least 75% from baseline at two weeks following the 12-week treatment period. Table 2 shows the treatment response in the first study of Cohort 1 and Study 2. Response to treatment in both studies was defined as the proportion of patients with a reduction in score on the Psoriasis Area and Severity Index (PSA) of at least 75% from baseline at two weeks following the 12-week treatment period.

In Study 1 (the Intravenous Study) and Study 2 (the Intramuscular Study) Two-week Post Dosing

Table 2. Percentage of Patients Responding to the First Course of Treatment in Study 1 (the Intravenous Study) and Study 2 (the Intramuscular Study)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>AMEVIVE® 7.5 mg IV (16)</th>
<th>AMEVIVE® 15 mg IM (16)</th>
<th>Placebo</th>
<th>AMEVIVE® 15 mg IM (16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in PASI</td>
<td>4%</td>
<td>14%</td>
<td>10 (14, 23)</td>
<td>5%</td>
<td>13%</td>
</tr>
<tr>
<td>&quot;Almost clear&quot; or &quot;clear&quot;</td>
<td>10%</td>
<td>19%</td>
<td>20 (22, 35)</td>
<td>18%</td>
<td>42%</td>
</tr>
</tbody>
</table>

In Study 2, the proportion of responders to the 10 mg IM dose was higher than placebo, but the difference was not statistically significant.

In both studies, onset of response to AMEVIVE® treatment (at least a 50% reduction of baseline PASI) began at least 60 days after the start of therapy. With one course of therapy in Study 1 (IV route), the median duration of response (defined as maintenance of a 75% or greater reduction in PASI) was 3.5 months for AMEVIVE®-treated patients and 1 month for placebo-treated patients. In Study 2 (IM route), the median duration of response was approximately 2 months for both AMEVIVE®-treated patients and placebo-treated patients.

Most patients who had responded to either AMEVIVE® or placebo maintained a 50% or greater reduction in PASI through the 3-month observation period. In responders Study 1 who received AMEVIVE® 7.5 mg IV or in Study 2 who received AMEVIVE® 15 mg IM were followed for additional treatment after AMEVIVE® retreatment, a 50% or greater reduction in PASI was maintained for a median of 7 months.

Some patients achieved their maximal response beyond 2 weeks post-dosing. In Studies 1 and 2, an additional 15% (42/287) and 7% (12/166) of patients treated with AMEVIVE® respectively, achieved a 75% reduction from baseline PASI score at one or more visits after the first 2 weeks of the follow-up period. In responders Study 1 who received AMEVIVE® 7.5 mg IV or in Study 2 who received AMEVIVE® 15 mg IM were followed for additional treatment after AMEVIVE® retreatment, a 50% or greater reduction in PASI was maintained for a median of 7 months.

Retreatment Patients in Study 1 who had completed the first IV treatment course were eligible to receive a second treatment course if their PASI was less than “clear” by PGA and their CD4 T lymphocyte count was above the lower limit of normal. The level of response (decrease in median PASI score) over the two courses of IV treatment is shown in Figure 1. The median reduction in PASI score was greater in patients who received a second course of AMEVIVE® treatment (see Cohort 1) compared to patients who received placebo (see Cohort 2).

Figure 1. Median PASI Score Over Time

In Study 2, patients who had responded to or had not responded to any course of treatment with AMEVIVE® were enrolled into a subsequent course of treatment. In study 2, patients who had responded to or had not responded to any course of treatment with AMEVIVE® were enrolled into a subsequent course of treatment.

In the 24-week period constituting the first course of placebo-controlled studies, 13 malignancies were diagnosed in 11 AMEVIVE®-treated patients. The incidence of malignancies was 1.3% (11/876) for AMEVIVE®-treated patients compared to 0.5% (2/413) in the placebo group (see ADVERSE REACTIONS, Malignancies). In preclinical studies, animals developed B cell hyperplasia, and one animal developed a lymphoma (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Fibrosis). AMEVIVE® should be discontinued if the patients develops a malignancy. AMEVIVE® should be discontinued if the patients develops a malignancy.

Serious Infections

AMEVIVE® is an immunosuppressive agent and, therefore, has the potential to increase the risk of infection and reactivate latent, chronic infections. AMEVIVE® should not be administered to patients with a clinically important infection. Caution should be exercised when considering the use of AMEVIVE® in patients with chronic infections or a history of recurrent infection. Patients should be monitored for signs and symptoms of infection during or after a course of AMEVIVE®. New infections should be closely monitored. If a patient develops a serious infection, AMEVIVE® should be discontinued (see ADVERSE REACTIONS, Infections).

PRECAUTIONS

Effects on the Immune System

Patients receiving other immunosuppressive agents or phototherapy should not receive concurrent therapy with AMEVIVE® because of the possibility of excessive immunosuppression. The safety and efficacy of vaccines, specifically live or live-attenuated vaccines, administered to patients being treated with AMEVIVE® have not been studied. In a study of 46 patients with chronic plaque psoriasis, the ability to mount an immune response (local antigen) and an experimental neo-antigen was preserved in those patients undergoing therapy with AMEVIVE®. Allergic Reactions

Hypersensitivity reactions (urticaria, angioedema) were associated with the administration of AMEVIVE®. If an anaphylactic reaction or other serious allergic reaction occurs, administration of AMEVIVE® should be discontinued immediately and appropriate therapy initiated.

Hepatic Injury

In post-marketing experience there have been reports of liver injury, including asymptomatic transaminase elevation, fatty infiltration of the liver, hepatitis, decompensation of cirrhosis with liver failure and acute liver failure. Two cases of liver failure were reported with concomitant alcohol use (see ADVERSE REACTIONS, Hepatic Injuries). In the 24-week period constituting the first course of placebo-controlled studies, 1.7% (15/876) of AMEVIVE®-treated patients and 1.2% (4/341) of the placebo group experienced ALT and/or AST elevations of at least 3 times the upper limit of normal. While the exact relationship of these occurrences with AMEVIVE® is not known, patients with signs or symptoms of liver injury should be fully evaluated. AMEVIVE® should be discontinued in patients who develop significant clinical signs of liver injury.

Information for Patients

Patients should be informed of the need for regular monitoring of white blood cell (lymphocyte) counts during therapy and that AMEVIVE® must be administered under the supervision of a physician. Patients should also be informed that AMEVIVE® reduces lymphocyte counts, which could increase their chances of developing an infection or a malignancy. Patients should be advised to inform their physician promptly if they develop any signs or symptoms of bacterial, fungal, or viral infections or develop a malignancy while undergoing a course of treatment with AMEVIVE®.

Female patients should be advised to notify their physicians if they become pregnant while taking AMEVIVE® for at least 8 weeks of discontinuing AMEVIVE® and be advised of the existence of and encouraged to enroll in the Pregnancy Registry. Call 1-866-AMEVIVE (1-866-263-8483) to enroll into the Registry (see PRECAUTIONS, Pregnancy).

Patients should be advised that serious liver injury has been reported in patients receiving AMEVIVE®. Patients should be advised to report to their physician persistent nausea, anorexia, fatigue, vomiting, abdominal pain, jaundice, easy bruising, dark urine or pale stools.

Laboratory Tests

The CD4 T lymphocyte counts should be monitored every two weeks during the 12-week AMEVIVE® dosing period and used to guide the dosing and duration of treatment. Concomitant CD4 T lymphocyte counts prior to an initial or a subsequent course of treatment with AMEVIVE®. If CD4 T lymphocyte counts are below 250 cells/µL, AMEVIVE® dosing should be withheld and very monitoring instituted. AMEVIVE® should be discontinued if CD4 T lymphocyte counts remain below 250 cells/µL for one month.
The data described below reflect exposure to AMEVIVE® in a total of 1869 psoriasis patients, of whom 876 received their first course in
1 of 3 or more courses of AMEVIVE®. Of the 1869 total patients, 78% were 50 years of age or older. Up to 75% of patients were 65 years of age or older.
One-year post-treatment there was no evidence of alefacept-related lymphopenia or B-cell hypoplasia in any of the remaining treated monkeys.

All animals in the study were positive for an endemic primate gammaherpesvirus also known as lymphocytotropic virus (LCV). LCV infection is generally asymptomatic, but can lead to B-cell lymphomas when animals are immune suppressed.

In a separate study, taboos given 3 doses of alefacept at 1 mg/kg/q1w every 4 weeks were found to have control.

Reproductive toxicology studies have been performed in cynomolgus monkeys at doses up to 5 mg/kg/wk (about 62 times the human dose based on body weight) and have revealed no evidence of impaired fertility or harm to the fetus due to ALFAVIRUS therapy. However, the potential for serious adverse reactions in nursing infants from AMEVIVE®, because there exists the potential for serious adverse reactions in nursing infants from AMEVIVE®,

It is not known whether AMEVIVE® is excreted in human milk. Because many drugs are excreted in human milk, nursing women should not be treated with AMEVIVE® unless the potential benefit justifies the potential risk to the infant.

The role of AMEVIVE® in the development of the lymphoid malignancy and the hyperplasia observed in human non-lymphoid malignancies is unknown. AMEVIVE®-treated patients compared to placebo-treated patients was chills (1% placebo compared to 0.5% (2/413) in the placebo group. In patients receiving repeated courses of AMEVIVE® therapy, the

rates of serious infections remained similar across courses of therapy. Serious infections among AMEVIVE® treated patients included: cellulitis, wound infections, toxic shock, pneumonia, appendicitis, cholecystitis, and herpes infections.

Hypersensitivity Reactions

In the intramuscular study (Study 2), 16% of AMEVIVE®-treated patients and 8% of placebo-treated patients reported rash reactions. In patients receiving repeated courses of AMEVIVE® IM therapy, the incidence of injection site reactions remained similar across courses of therapy. Reactions at the site of injection were mild to moderate and occurred in 32% of patients receiving repeated doses of AMEVIVE® therapy. For the bleeding (4%), edema (2%), non-specific reaction (2%), mass (1%), and skin hypersensitivity (<1%). In the clinical trials, a single case of injection site reaction led to the discontinuation of AMEVIVE® therapy.

Interim response data from treated patients (0.75 mg/kg qw) was associated with chickens, headache, asthma, and sinusitis within one day of dosing. Patients who had inadvertently been administered an excess of the recommended dose should be closely monitored for effects on total lymphocyte count and CD4+ T lymphocyte count.

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