FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Oncologic Drugs Advisory Committee (ODAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland 20993
May 24, 2017

QUESTIONS

NDA 208587
L-glutamine powder
Applicant: Emmaus Medical, Inc.

PROPOSED INDICATION: For the treatment of sickle cell disease (SCD).

EFFICACY

A phase 3 randomized, multicenter, double-blind, placebo-controlled study (Study GLUSCC09-01) was conducted in patients with SCD or sickle ß^0-thalassemia aged 5 years and older. Patients with at least 2 episodes of painful crises within the 12 months prior to screening were randomized (2:1) to receive oral L-glutamine 0.3 mg/kg/day or placebo for 48 weeks followed by a 3-week tapering period. Randomization was stratified by baseline hydroxyurea (HU) use and study site. Demographic characteristics were comparable in the two treatment arms. Most patients were also taking HU.

The primary efficacy analysis compared frequency of sickle cell crises through Week 48 and prior to start of taper between the two treatment arms. A sickle cell crisis was defined as a visit to an emergency room/medical facility for SCD-related pain that was treated with a parenterally administered narcotic or parenterally administered Toradol (ketorolac). Occurrences of acute chest syndrome, priapism, and splenic sequestration were also considered sickle cell crises even if the symptoms were not painful enough to require narcotics. All reported sickle cell crises were centrally adjudicated.

The Applicant's analysis revealed the median number of sickle cell crisis events was 3 for the L-glutamine arm and 4 for the placebo arm (p=0.0052). The statistical analysis of the efficacy results was complicated by differences in study discontinuation rates by treatment arm before completion of the full 48-week treatment period, which necessitated invocation of imputation methods. The rates of premature discontinuations between treatment arms were 36% in the L-glutamine arm and 24% in the placebo arm. Multiple explorations of ways to handle the missing data yielded findings which favored the L-glutamine treatment arm. However, all methods had limitations. FDA's exploration of approaches to handling the differential dropout rate found that in all the analyses the trend favored L-glutamine over placebo with a range of reduction in rates of crises per 48 weeks from 0.4 to 0.9. The phase 2 study with similar design (Study 10478), which failed to meet its specified significance level for primary efficacy analysis, also showed a trend in favor of L-glutamine over placebo.

QUESTIONS (cont.)

SAFETY

The safety population for the indication included 187 patients treated with L-glutamine and 111 patients treated with placebo in the Phase 2 study (10478) and the Phase 3 study (GLUSCC09-01). During the study most patients experienced a treatment-emergent serious adverse event, most commonly sickle cell anemia with crisis (66.3% of patients treated with L-glutamine and 72.1% of patients treated with placebo) and acute chest syndrome (7.0% of patients treated with L-glutamine and 18.9% of patients treated with placebo). Treatment emergent adverse events (TEAE) led to withdrawal from study in 2.7% of L-glutamine treated patients and 0.9% of placebo treated patients. The safety review revealed that the most common adverse reactions (incidence ≥ 10% and greater than placebo) were constipation, nausea, headache, cough, pain in extremity, back pain, chest pain, and abdominal pain.

QUESTION

1. **VOTE:** Based on the available data presented and discussed, is the overall benefit-risk profile of L-glutamine for the treatment of sickle cell disease favorable?