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
May 14, 2019

QUESTIONS

NDA 211810
Pexidartinib
Applicant: Daiichi-Sankyo, Inc.

PROPOSED INDICATION: Treatment of adult patients with symptomatic tenosynovial giant cell tumor also referred to as giant cell tumor of the tendon sheath or pigmented villonodular synovitis, which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.

BACKGROUND

Tenosynovial giant cell tumor (TGCT) is a rarely malignant tumor involving the synovium, bursae, or tendon sheath which can be locally aggressive and debilitating in some patients. Surgical resection is the primary treatment; however, in patients whose disease is not amenable to surgical resection, treatment options are limited as there are no approved systemic therapies for this disease.

EFFICACY

ENLIVEN is a randomized (1:1), double-blind, placebo-controlled trial, conducted in patients with TGCT not amenable to surgical resection. The primary efficacy outcome measure was overall response rate (ORR) at Week 25 as assessed by blinded independent central review (BICR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. ENLIVEN was designed to enroll a total of 126 patients to provide 90% power to detect a difference in ORR at a two-sided alpha level of 0.05, assuming an ORR of 10% in the placebo arm and an ORR of 35% in the pexidartinib arm.
A hierarchical procedure was specified in the analysis plan to adjust for multiplicity in testing the secondary efficacy outcomes in the order listed below:

1. Mean change from baseline in range of motion (ROM) of the affected joint, relative to a reference standard for the same joint at Week 25
2. Proportion of responders based on a 50% reduction in tumor volume score (TVS) at Week 25 as measured in centrally evaluated MRI scans
3. Mean change from baseline score in the Patient-Reported Outcomes Measurement Information System (PROMIS®) Physical Function Scale at Week 25
4. Mean change from baseline score in the Worst Stiffness numeric rating scale (NRS) item at Week 25
5. Proportion of responders based on patients who experienced a decrease of at least 30% in the mean Brief Pain Inventory (BPI) Worst Pain NRS item and did not experience a $\geq$ 30% increase in narcotic analgesic use (BPI-30) at Week 25

ENLIVEN demonstrated a statistically significant improvement in ORR in the pexidartinib arm compared to the placebo arm: ORR: 39% (95% CI: 28, 52) for pexidartinib compared to 0% (95% CI: 0, 6) for placebo; p-value <0.0001. Of the patients with a confirmed response, only one had progressive disease in follow-up.

There were also statistically significant improvements in the secondary endpoints of mean change in ROM, ORR per TVS, mean change in physical function per PROMIS®, and mean change in worst stiffness for patients randomized to the pexidartinib arm compared to patients randomized to the placebo arm. There was no statistically significant difference between treatment arms for BPI-30.

QUESTIONS (cont.)

ISSUE #1: Although ENLIVEN demonstrated a statistically significant improvement in the COA endpoints of mean change in ROM, physical function, and worst stiffness, the estimation of clinical benefit based on these results is limited due to the following: the high proportion of patients with missing assessments, changes in the statistical analysis plan for testing of these endpoints, potential unblinding due to hair color changes in a majority of patients who received pexidartinib, and limitations in establishing a clinically meaningful threshold of benefit for ROM.

SAFETY
The most common (≥20% of patients) adverse reactions of pexidartinib in the ENLIVEN trial were changes in hair color, fatigue, increased aspartate aminotransferase (AST), eye/facial edema, increased alanine aminotransferase (ALT), rash, dysgeusia, and vomiting. Serious adverse events occurred in 13% patients and 13% of patients experienced an adverse reaction that resulted in permanent discontinuation of pexidartinib. The most common adverse reactions (≥2 patients) leading to discontinuation of pexidartinib were increased ALT, increased AST and hepatotoxicity. Thirty-three percent of patients required dose interruptions. The most common (>5% of patients) adverse reactions leading to dose interruptions of pexidartinib were increased AST, increased ALT, increased alkaline phosphatase, and nausea.

ISSUE #2: In the ENLIVEN trial, ALT, AST, and total bilirubin elevations occurred in 67%, 90%, and 12% of patients, respectively, with Grade ≥3 severity in one third of patients. In the ENLIVEN trial, 4.9% (upper bound of the 95% CI: 13.7%) of patients had laboratory abnormalities indicative of drug induced liver injury (i.e., a total bilirubin of greater than or equal to 2 times [x] the upper limit of normal [ULN] and an AST or ALT greater than or equal to 3 x ULN). This pattern was consistent with that observed in a pooled analysis of all TGCT patients in the pexidartinib development program (N=130). The majority of patients in the TGCT population who experienced transaminase elevations and total bilirubin increase had improvement to baseline levels with dose reductions, dose interruption, and/or discontinuation of pexidartinib.

Across the overall development program (commercial-sponsored and investigator-initiated trials), two of 768 pexidartinib-treated patients (observed rate 0.3%; upper bound of the 95% CI: 0.9%) experienced irreversible liver injury, resulting in liver transplantation in one patient and death in another. Biopsies obtained in a limited number of patients with liver injury reveal a pattern of hepatocellular injury as well as injury to bile ducts/ ductopenia.

Uncertainties remain regarding the mechanism of action and course of injury to bile ducts (e.g., whether progressive, whether occurs in setting of normal/normalized transaminase levels), whether pexidartinib causes subacute or chronic injury, which may result in cirrhosis and liver, and what the effects of long-term exposure to pexidartinib are.

QUESTIONS

1. **DISCUSSION:** Discuss whether the benefits of pexidartinib, as characterized by a clinically meaningful reduction in tumor burden and an improvement in range of motion, outweigh its risk of hepatoxicity.

2. **VOTE:** Does the demonstrated benefit of pexidartinib outweigh the risks of the drug in the proposed indication?