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
April 12, 2016

DRAFT QUESTIONS

NDA 208542

Rociletinib tablets

APPLICANT: Clovis Oncology, Inc.

PROPOSED INDICATION: For the treatment of patients with mutant epidermal growth factor receptor (EGFR) non-small cell lung cancer (NSCLC) who have been previously treated with an EGFR-targeted therapy and have the EGFR T790M mutation as detected by an FDA approved test.

- Two non-randomized studies support the efficacy and safety findings in the proposed indication: Studies CO-1686-008 and CO-1686-019.
- Clinical Pharmacology Summary
    - There is high variability in systemic exposure to rociletinib and its major metabolites, M502 (which induces hyperglycemia) and M460 (which induces QTc prolongation).
    - Exposure-response analyses indicate a plateau in ORR at exposures obtained with rociletinib at doses ranging from 500 mg BID to 1000 mg BID.
    - The major metabolites of rociletinib, M502 and M460 are metabolized by N-acetyltransferase (NAT2). Patients who are classified as NAT2 slow acetylators based on NAT2 genotype have increased M502 and M460 exposures. In exposure-safety analyses, there is an increased risk for QTc prolongation and hyperglycemia with increasing exposure to M502 and M460, respectively.
- Efficacy Summary

  In a pooled analysis of patients with metastatic EGFR T790M mutation positive NSCLC who have been previously treated with an EGFR-targeted therapy and who received rociletinib at doses of 500 mg, 625 mg, and 750 mg BID:
    - the objective response rate per RECIST v1.1, as assessed by an IRC, is 30.2% (95% CI 25.2, 35.5)
    - the median duration of response per RECIST v1.1, as assessed by an IRC is 8.9 months (95% CI: 7.2, 12.9)

DRAFT QUESTIONS (cont.)

- Safety Summary
  - The most common (≥ 30%) treatment emergent adverse events in patients who received rociletinib were hyperglycemia (58%), diarrhea (55%), nausea (52%), fatigue (44%), decreased appetite (36%), QT prolongation (33%), and vomiting (30%).
    - The incidence of Grade 3 or 4 hyperglycemia was 34%.
    - The incidence of Grade 3 or 4 QT prolongation was 11%.
  - Serious adverse events observed in ≥ 2% of patients were hyperglycemia (9%), pneumonia (5%), pancreatitis (2%), nausea (2%), vomiting (2%), and diarrhea (2%).
    - There were 2 sudden deaths.
    - There were 3 cases of ventricular tachyarrhythmia and 1 case of Torsade de pointes.
  - The incidence of dose reduction was 51%, dose interruption was 56%, and discontinuation of rociletinib for adverse reactions was 21%.

1. **DISCUSSION**: Please discuss whether the benefit-risk profile of rociletinib is favorable in the proposed population.

2. **VOTE**: Should the results of the randomized clinical trial (TIGER-3) be submitted before FDA makes a regulatory decision on this application?