FINAL 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)
• 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?