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Draft Guidance on Repotrectinib

May 2025

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Active Ingredient: Repotrectinib

Dosage Form: Capsule

Route: Oral

Strengths: 40 mg, 160 mg

Recommended Studies: Three in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 160 mg
   Subjects: Healthy males and healthy females not of reproductive potential
   Additional comments: Exclude subjects with abnormal liver function tests. Males with female partners of reproductive potential should use effective contraception during the study and for four months after the last dose. Subjects should be evaluated prior to discharge for cognitive impairment such as somnolence and dizziness and instructed not to drive or operate machinery until their cognitive function returns to baseline level. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of repotrectinib. Alternatively, a parallel study design may be considered. $AUC_{(0\text{-}72h)}$ may be used in place of $AUC_{(0\text{-}t)}$ for comparison of the extent of absorption.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 160 mg
Subjects: Healthy males and healthy females not of reproductive potential
Additional comments: See comments above. In vivo testing of the 160 mg strength under the fed conditions may be waived based on (i) an acceptable bioequivalence study under fasting conditions, (ii) acceptable in vitro dissolution testing between the test product and reference listed drug (RLD), and (iii) the same product design as the RLD, including the critical excipient(s) (e.g., excipients functioning as a solubilizing agent) that may pose bioinequivalence risk under fed conditions. Additionally, the quantity of the critical excipient(s) should not differ by more than 10% (w/w) from the RLD.

3. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 40 mg
Subjects: Healthy males and healthy females not of reproductive potential
Additional comments: See comments above. In vivo testing of the 40 mg strength may be waived based on (i) an acceptable bioequivalence study(ies) on the 160 mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) formulation qualitatively similar and the amount of critical excipient(s) directly proportional between the two strengths (i.e., critical excipient-to-active pharmaceutical ingredient weight ratios are the same).

Analyte to measure: Repotrectinib in plasma

Bioequivalence based on (90% CI): Repotrectinib

Waiver request of in vivo testing: See comments above.

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of both strengths of the test product and RLD.[1] Specifications will be determined upon review of the abbreviated new drug application.

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Unique Agency Identifier: PSG_218213

[1] If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions.*