

## **Draft Guidance on Crizotinib**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active ingredient:** Crizotinib

**Form/Route:** Capsule/Oral

**Recommended studies:** 2 studies

1. Type of study: Fasting  
Design: Single-dose, two-way crossover in vivo  
Strength: 250 mg  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments: Study population should consist of healthy subjects 18 to 70 years old with no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure (BP) and pulse rate (PR) measurement, 12-lead electrocardiogram (ECG) and clinical laboratory tests.

To minimize risks, based on the current knowledge, the following exclusion criteria are recommended (the sponsor may add others):

1. Age < 18 or > 70 years
2. Pregnant or breastfeeding women
3. Women of childbearing potential
4. Individuals with hepatic or renal dysfunction
5. Current use or anticipated need for drugs with known or suspected interactions with Crizotinib
6. Subjects with hypertension or cardiovascular risk factors

The following safety monitoring (prior to dosing and after each dosing period) are recommended during the BE trial: pregnancy test for women, liver function tests, electrocardiogram, urinalysis, pulse rate, and blood pressure. In addition, males and their female partners need to practice adequate contraception for at least two weeks after the last dose of Crizotinib.

The following stopping rules are recommended: occurrence of two or more adverse events of > Grade 2 (Common Terminology Criteria for Adverse Events (CTCAE) or WHO Toxicity Criteria), any occurrence of > CTCAE Grade 3 adverse events, or any occurrence of a serious adverse event (SAE) that is possibly related to the study drug.

2. Type of study: Fed  
Design: Single-dose, two-way crossover in vivo  
Strength: 250 mg  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments: Please see comments above.
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**Analytes to measure (in appropriate biological fluid):** Crizotinib in plasma

**Bioequivalence based on (90% CI):** Crizotinib

**Waiver request of in vivo testing:** 200 mg based on (i) acceptable bioequivalence studies on the 250 mg strength, (ii) acceptable in vitro dissolution testing of 200 mg and 250 mg strengths, and (iii) proportional similarity of the formulations across 200 mg and 250 mg strengths.

**Dissolution test method and sampling times:**

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.