> The actual effect of **multiple doses of VX-770 150 mg and 450 mg on QTc was evaluated in Part B**; a double-blind, randomized, placebo- and active-controlled … study in which 72 subjects received VX-770 150 mg q 12h, VX-770 450 mg q 12h, placebo, and moxifloxacin 400 mg (the active comparator). The … supra-therapeutic dose of 450 mg q 12h produced mean Cmax approximately 4 times higher than the mean Cmax for the therapeutic dose of 150 mg q 12h. No significant QTc prolongation effect of VX-770 at the doses tested was detected.

i. Clinical Study Protocol's Instructions for QT Interval Testing for a Clinical Trial on Cystic Fibrosis

The Clinical Study Protocol used for a study on *ivacaftor*, a drug for treating cystic fibrosis, provides instructions relating to QT interval (176,177). This Protocol is related to the NDA that is described in the preceding paragraphs. The relationship between the NDA and this Protocol is demonstrated by the timeline outlined in footnote (178).

Excerpts from this Protocol illustrated the drug discontinuation instructions:

> If the QTc value remains above the threshold value (greater than 45 msec from the average of the 3 predose values on Day 1 or greater than 500 msec) on repeated measurement or is noted on greater than 2 occasions with no identified alternative etiology for the increased QTc study drug, then discontinuation from study drug treatment may be required after discussion with the medical monitor. Subjects in whom treatment is discontinued for increased QTc should have their QTc monitored closely until it normalizes or returns to baseline.

The Protocol also discloses Fridericia's correction as well as Bazett's correction, for use in the analysis of the ECG data:

> A cardiologist … will review each ECG to confirm if intervals were calculated correctly and to provide an interpretation, including a suggested clinical significance, as applicable … [t]he values reported by the central ECG diagnostic service will be used for data analysis. The PR, QT, and QTc for HR intervals (including **Fridericia's correction** [$QTcF = QT/RR^{1/3}$] and **Bazett's correction** [$QTcB = QT/RR^{0.50}$]), QRS duration, and HR will be captured in the ECG database.

j. The Electrocardiogram

The electrocardiogram (ECG) is used for diagnosing intraventricular conduction disturbances and arrhythmias. ECG readings are used for detecting electrolyte abnormalities, particularly of serum potassium and calcium, for detecting genetic cardiac abnormalities, and for monitoring patients treated with antiarrhythmic drugs and noncardiac drugs. The American Heart Association has issued a series of six guidelines for conducting and interpreting ECGs for different patient groups (179). ECG measurements are

[176]Clinical Study Protocol. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous for the *F508del-CFTR* Mutation. Vertex Study Number: VX12-809-103. Lumacaftor IND Number: 79,521. Ivacaftor IND Number: 74,633. EUDRACT Number: 2012-003989-40. Date of Protocol: 05 February 2014 (Version 3.0) Replaces Version 2.0, dated 25 July 2013.

[177]The Clinical Study Protocol was provided as a supplement to Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del *CFTR*. New. Engl. J. Med. 2011;365:1663–72.

[178]First, the Sponsor submitted an Investigational New Drug (IND) application (IND No. 74,633). The Clinical Study Protocol, that is, Protocol No. VX12-809-103, was part of this submitted IND. FDA's review of this IND referred to VX12-809-103.

[179]Kligfield P, Gettes GS, Bailey JJ, et al. Recommendations for the standardization and interpretation of the electrocardiogram. Part I: The electrocardiogram and its technology. Circulation 115:1306–24.