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Effect of VX-770 in Persons with Cystic Fibrosis and the G551D-*CFTR* Mutation

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Abstract

BACKGROUND—A new approach in the treatment of cystic fibrosis involves improving the function of mutant cystic fibrosis transmembrane conductance regulator (CFTR). VX-770, a CFTR potentiator, has been shown to increase the activity of wild-type and defective cell-surface CFTR in vitro.

METHODS—We randomly assigned 39 adults with cystic fibrosis and at least one G551D-*CFTR* allele to receive oral VX-770 every 12 hours at a dose of 25, 75, or 150 mg or placebo for 14 days (in part 1 of the study) or VX-770 every 12 hours at a dose of 150 or 250 mg or placebo for 28 days (in part 2 of the study).

RESULTS—At day 28, in the group of subjects who received 150 mg of VX-770, the median change in the nasal potential difference (in response to the administration of a chloride-free isoproterenol solution) from baseline was −3.5 mV (range, −8.3 to 0.5; P = 0.02 for the within-subject comparison, P = 0.13 vs. placebo), and the median change in the level of sweat chloride was −59.5 mmol per liter (range, −66.0 to −19.0; P = 0.008 within-subject, P = 0.02 vs. placebo). The median change from baseline in the percent of predicted forced expiratory volume in 1 second was 8.7% (range, 2.3 to 31.3; P = 0.008 for the within-subject comparison, P = 0.56 vs. placebo).

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None of the subjects withdrew from the study. Six severe adverse events occurred in two subjects (diffuse macular rash in one subject and five incidents of elevated blood and urine glucose levels in one subject with diabetes). All severe adverse events resolved without the discontinuation of VX-770.

CONCLUSIONS—This study to evaluate the safety and adverse-event profile of VX-770 showed that VX-770 was associated with within-subject improvements in CFTR and lung function. These findings provide support for further studies of pharmacologic potentiation of CFTR as a means to treat cystic fibrosis.

Cystic fibrosis is a progressive lung disease[1] caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein, an epithelial ion channel involved in salt and fluid transport in multiple organs, including the lung.[2,3] Current treatments for cystic fibrosis target the secondary effects of CFTR dysfunction. Although the median predicted survival among patients with cystic fibrosis has improved,[4] the life expectancy of these patients remains well below normal, and the treatment burden to maintain health is high,[5] indicating a need for better therapies. A strategy with potential advantages over current regimens involves improving defective CFTR function systemically; this strategy aims to slow lung damage and reduce the manifestations of extrapulmonary disease and the treatment burden.[6]

Some mutations permit CFTR protein to reach the epithelial-cell surface, but the protein is defective in chloride transport.[7] The most prevalent mutation of this type in patients with cystic fibrosis causes a substitution of glycine for aspartic acid at amino acid 551 (G551D-CFTR); this mutation occurs in approximately 4 to 5% of persons with cystic fibrosis.[4] Agents that increase the ion-channel function of activated cell-surface CFTR are referred to as “potentiators.” VX-770 is an investigational, orally bioavailable CFTR potentiator that has been shown to increase the activity of wild-type and defective cell-surface CFTR protein in vitro.[8] The greatest effect of VX-770 was on cells with G551D-CFTR.

The primary end points of this randomized, placebo-controlled trial involving subjects with the G551D-*CFTR* mutation were the safety and adverse-event profile of VX-770. Evidence of improvement in CFTR-mediated ion transport and pulmonary status were evaluated as secondary end points.

METHODS

Part 1 of this two-part, double-blind, placebo-controlled, multicenter, phase 2 trial had a modified crossover design, and part 2 had a parallel design (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol (available at NEJM.org) was reviewed and approved by the institutional review board in each participating center, and each subject provided written informed consent. Subjects had to be 18 years of age or older and have cystic fibrosis,[9] a G551D mutation on at least one *CFTR* allele, and a forced expiratory volume in 1 second (FEV_1) of 40% or more of the predicted value for age, sex, and height.[10]

The first author wrote the first draft of the manuscript and made the decision to submit the article for publication after consultation with the other authors. All authors vouch for the accuracy and completeness of the reported data. The authors also certify that the study as reported conforms with the protocol.

Part 1 of the study involved subjects who were randomly assigned to receive VX-770 every 12 hours at doses of 25, 75, or 150 mg or placebo. The study drug was administered during two 14-day periods separated by a washout period. Part 2 of the study involved new subjects

who were randomly assigned to receive VX-770 every 12 hours at a dose of 150 or 250 mg or placebo for 28 consecutive days.

The primary objective was to evaluate the safety and adverse-event profile of VX-770. Secondary end points included assessment of biomarkers of CFTR ion-channel function, pulmonary function, and health-related quality of life. The CFTR chloride transport function was evaluated in the airway epithelium on the basis of the nasal potential difference[11] and outside the respiratory tract on the basis of the sweat chloride concentration. Clinical efficacy was evaluated on the basis of the change in the FEV_1 from baseline and a disease-specific health-related quality-of-life instrument, the Cystic Fibrosis Questionnaire–revised (CFQ-R) (in part 2 of the study only).[12] Each CFQ-R domain is scored on a 100-point scale, with higher scores indicating a lower effect of symptoms on the patient's quality of life. A minimal clinically important difference of 4 points has been determined for the respiratory symptoms domain.[13]

Further details of the study design, measurement of biomarkers and lung function, and the health-related quality-of-life instrument are provided in the Supplementary Appendix.

RESULTS

SUBJECTS

Twenty subjects received a study drug in part 1 of the study, and 19 subjects received a study drug in part 2. The baseline characteristics of the subjects are shown in Table 1. The sex distribution was well balanced, and the body-mass index and other relevant baseline clinical and demographic characteristics were similar between the groups in each part of the study. The median rate of adherence to treatment was high among subjects in both parts of the study (96.4% [range, 60.7 to 100] in part 1 and 100% [range, 92.6 to 100] in part 2).

SAFETY AND ADVERSE-EVENT PROFILE

All subjects who began to receive a study drug completed the assigned study drugs (randomization and study-drug assignments are shown in Fig. 2 in the Supplementary Appendix). The frequency of adverse events was similar between the groups and between the parts of the study. Most adverse events were reported in one or two subjects in any group, with more frequent events being fever (in four subjects in the group of subjects who received 75 mg of VX-770); cough (in three subjects in the placebo group in part 1 of the study and in three subjects who received 250 mg of VX-770 in part 2 of the study); and nausea, pain, and rhinorrhea (in three subjects each in the group of subjects who received 75 mg of VX-770). All adverse events are listed in Table 1 in the Supplementary Appendix.

Adverse events that were considered moderate (grade 2) or severe (grade 3) are shown in Table 2. Six adverse events were severe; all occurred during part 1 of the study. These events consisted of diffuse macular rash in one subject who was receiving VX-770 at a dose of 150 mg and an elevated blood glucose level on three occasions (two occurred within the same treatment period and were counted once in Table 2) and urine that was positive for glucose on two occasions in one subject over both treatment periods (VX-770 at doses of 75 mg and 150 mg). The subject in whom the macular rash developed had received intravenous antibiotics during hospitalization to treat a mild pulmonary exacerbation. The pulmonary exacerbation and macular rash in this subject were the only adverse events in the study that met the definition of serious adverse events. The subject in whom elevated blood and urine glucose levels developed had a history of insulin-dependent diabetes. All serious or severe adverse events resolved without discontinuation of the study drug.

CFTR ION-CHANNEL FUNCTION

We evaluated the effects of VX-770 on measurements of the potential difference across the nasal mucosa and on the chloride concentration of sweat, both markers of CFTR function. Figure 1 shows the nasal potential difference (in response to the administration of a chloride-free isoproterenol solution), a measure of CFTR-mediated chloride transport. In part 1 of the study, significant within-subject changes from baseline to day 14 were observed in the VX-770 75-mg group (mean, −4.7 mV; 95% confidence interval [CI], −7.5 to −1.9; P=0.003) and in the 150-mg group (mean, −5.4 mV; 95% CI, −9.3 to −1.6; P = 0.01). No significant change from baseline was detected in the placebo group (−1.7 mV; 95% CI, −6.1 to 2.6; P = 0.41) or the VX-770 25-mg group (−1.6 mV; 95% CI, −5.6 to 2.5; P = 0.43). None of the changes from baseline were significant as compared with the placebo group (P = 0.95, P = 0.24, and P = 0.21 for the VX-770 25-mg, 75-mg, and 150-mg groups, respectively). In part 2 of the study, the median within-subject change from baseline to day 28 was significant in the VX-770 150-mg group (−3.5 mV; range, −8.3 to 0.5; P = 0.02) and the 250-mg group (−5.5 mV; range, −28.5 to 2.0; P = 0.05), but not in the placebo group (−0.4 mV; range, −2.3 to 4.0; P = 0.88). In the VX-770 treatment groups, the changes from baseline were not significantly different from placebo (P = 0.13 and P = 0.16 in the VX-770 150-mg and 250-mg groups, respectively). Responses in the VX-770 treatment groups were similar to baseline values after the washout period in part 1 of the study (Fig. 3 in the Supplementary Appendix).

After 14 days of treatment with VX-770, some subjects for whom data were available in parts 1 and 2 of the study were considered to have had a response according to the predefined response criterion of a decrease from baseline of 5 mV or more in the nasal potential difference after the administration of a chloride-free isoproterenol solution. These subjects were the following: 1 of 7 in the 25-mg group (14%), 5 of 15 in the 75-mg group (33%), 10 of 16 in the 150-mg group (62%), and 3 of 7 in the 250-mg group (43%). None of the subjects had a response in the placebo group. We observed significant improvements in sodium transport, as measured by the basal and amiloride responses in the nasal potential difference, in part 1 but not in part 2 of the study (Table 2 in the Supplementary Appendix).

The change in the sweat chloride concentration from baseline is shown in Figure 2 (the actual sweat chloride concentrations at days 14 and 28 are shown in Fig. 4 in the Supplementary Appendix). In part 1 of the study, the mean change in the sweat chloride concentration from baseline to day 14 was −32.9 mmol per liter (95% CI, −42.4 to −23.3) in the group that received 25 mg of VX-770, −40.4 mmol per liter (95% CI, −48.7 to −32.2) in the group that received 75 mg of VX-770, and −42.3 mmol per liter (95% CI, −52.8 to −31.8) in the group that received 150 mg of VX-770. The changes were significant (P<0.001) in both within-subject comparisons and versus placebo in all VX-770 groups. The mean change from baseline in the placebo group was 4.4 mmol per liter (95% CI, −10.4 to 19.1; P = 0.53). In part 2, the median change from baseline to day 28 was −59.5 mmol per liter (range, −66.0 to −19.0) in the VX-770 150-mg group and −38.0 mmol per liter (range, −47.0 to −10.5) in the VX-770 250-mg group. Results in both VX-770 groups were significant for within-subject comparisons (P = 0.008 for VX-770 at a dose of 150 mg and P = 0.02 for VX-770 at a dose of 250 mg) and versus placebo (P = 0.02 for the VX-770 150-mg group and P = 0.03 for the VX-770 250-mg group). Over the same time frame, the median change from baseline in the placebo group was 5.0 mmol per liter (range, −2.0 to 11.0; P = 0.38). Sweat chloride concentrations in the VX-770 treatment groups returned toward baseline concentrations after the washout period in part 1 of the study (Fig. 3 in the Supplementary Appendix). Considering parts 1 and 2 of the study together, after 14 days, the number of subjects with available data who achieved the prespecified response criterion of a decrease from baseline of 20 mmol per liter or more was 6 of 8 subjects in the VX-770 25-mg group (75%), 11 of 13 subjects in the VX-770 75-mg group (85%), 13 of 14 subjects

in the VX-770 150-mg group (93%), and 4 of 7 subjects in the VX-770 250-mg group (57%). No subjects had a response in the placebo group.

SPIROMETRIC ASSESSMENTS

Results of the absolute FEV_1 in liters and the relative percentage change in the predicted FEV_1 are shown in Figure 3. Results of other spirometric measurements are provided in Figures 5, 6, and 7 in the Supplementary Appendix. In part 1 of the study, at day 14, the mean within-subject change in FEV_1 from baseline was 0.09 liters (95% CI, −0.06 to 0.24) in the VX-770 25-mg group, 0.19 liters (95% CI, 0.08 to 0.29) in the VX-770 75-mg group, and 0.22 liters (95% CI, 0.08 to 0.36) in the VX-770 150-mg group. In the placebo group, the mean change was −0.03 liters (95% CI, −0.20 to 0.15). Improvements in the VX-770 75-mg and 150-mg groups were significant for within-subject change (P = 0.003 and P = 0.006, respectively) and as compared with placebo (P=0.05 and P=0.04, respectively); changes were not significant in the VX-770 25-mg group (P = 0.19 for the within-subject change, P=0.28 vs. placebo) and placebo group (P=0.76 for the within-subject change). Among the subjects who received VX-770, the mean relative change from baseline in the percentage of predicted FEV_1 was 4.9% (95% CI, −2.6 to 12.5) in the 25-mg group, 10.0% (95% CI, 4.5 to 15.6) in the 75-mg group, and 10.5% (95% CI, 3.3 to 17.7) in the 150-mg group. The mean change in the placebo group was 0.7% (95% CI, −8.8 to 10.2). Within-subject improvements in the percentage of predicted FEV_1 were significant in the VX-770 75-mg and 150-mg groups (P = 0.002 and P = 0.008, respectively), but not in the VX-770 25-mg or placebo groups (P = 0.18 and P = 0.88, respectively). Differences in comparisons with the placebo group did not reach significance (P = 0.45, P = 0.09, and P=0.10, respectively, for the VX-770 25-mg, 75-mg, and 150-mg groups).

In part 2 of the study, at day 28, the median within-subject change from baseline in FEV_1 was 0.25 liters (range, 0.05 to 0.75) in the VX-770 150-mg group, 0.17 liters (range, 0 to 0.37) in the VX-770 250-mg group, and 0.20 liters (range, 0.12 to 0.33) in the placebo group. The within-subject change was significant in both VX-770 treatment groups (P = 0.008 and P = 0.03 for 150 mg and 250 mg, respectively), but not in the placebo group (P = 0.38). Comparisons between the treatment and placebo groups were not significant (P = 1.0 and P = 0.65 for 150 mg and 250 mg of VX-770, respectively). The median relative change from baseline in the percentage of predicted FEV_1 was 8.7% (range, 2.3 to 31.3; within-subject comparison, P = 0.008) in the VX-770 150-mg group and 4.4% (range, 0 to 18.3; within-subject comparison, P=0.03) in the 250-mg group. In the placebo group, although there was an improvement from baseline of 7.3% (range, 5.2 to 8.2), this difference did not achieve statistical significance (within-subject comparison, P=0.13). Comparisons between the treatment and placebo groups were not significant (P = 0.56 and P = 0.78 for 150 mg and 250 mg of VX-770, respectively).

The combined part 1 and part 2 data for the change from baseline to day 14 of study treatment for spirometric analysis and CFTR biomarkers (nasal potential difference and sweat chloride concentration) are shown in Figure 8 in the Supplementary Appendix.

HEALTH-RELATED QUALITY OF LIFE

The CFQ-R was administered in part 2 of the study only (Table 3 in the Supplementary Appendix). No change from baseline in any CFQ-R domain was significant. After 14 days of treatment, subjects reported median improvements from baseline in the respiratory domain of 5.6 points (range, 0 to 16.7; P = 0.06 within-subject) in the VX-770 150-mg group, 5.6 points (range, −11.1 to 11.1; P = 0.16) in the VX-770 250-mg group, and 2.8 points (range, −5.6 to 11.1; P = 0.75) in the placebo group. Comparisons between the treatment and placebo groups were not significant (P = 0.61 and P = 0.71 for the VX-770

150-mg and 250-mg groups, respectively). At day 28, the median improvements from baseline were 8.3 points (range, 0 to 16.7; P=0.06 within-subject) in the VX-770 150-mg group and 11.1 points (range, −5.6 to 33.3; P = 0.08) in the 250-mg group, whereas scores in the placebo group were identical to those at day 14. Comparisons between the treatment and placebo groups were not significant (P = 0.45 and P = 0.47 for the VX-770 150-mg and 250-mg groups, respectively).

DISCUSSION

This randomized, double-blind, placebo-controlled, multicenter trial of oral VX-770 involved subjects with cystic fibrosis and the G551D mutation on at least one allele. The primary end points of the study were safety and the adverse-event profile associated with treatment. No subject withdrew from the study, and the frequency of adverse events was similar between the study groups. The safety profile of VX-770 in this study provides support for further clinical evaluation. In addition, VX-770 was associated with within-subject improvements in CFTR ion-channel function in the nasal epithelium and sweat glands and within-subject improvements in lung function, suggesting a potential clinical benefit. The findings in the nasal potential difference and sweat chloride biomarkers associated with VX-770 are consistent with improved CFTR ion-channel function. Previous studies of agents aimed at improving CFTR function, including oral and topical drug candidates as well as topically applied gene-therapy vectors, showed improvement in measures of chloride transport in the nasal potential difference,[14–17] but they did not measure sweat chloride concentrations. Single-center studies of oral lithium and of intravenous gentamicin have shown decreases in sweat chloride concentrations.[18,19] The study of gentamicin also showed an improvement in the nasal potential difference.[19] The current placebo-controlled, multicenter trial showed within-subject improvement in both the nasal potential difference and sweat chloride concentrations. Administration of VX-770 resulted in a much greater reduction in sweat chloride levels than has been observed with other compounds; sweat chloride levels in some subjects were outside the diagnostic range for cystic fibrosis after VX-770 treatment.

VX-770 was associated with a modest but significant within-subject improvement in lung function after 14- and 28-day treatment regimens. Improvement at day 28 in the groups of subjects who received VX-770 was similar to that at day 14, and the improvements were statistically significant within the treatment group. The change in FEV_1 was not significant among subjects who received placebo in part 1 and part 2 of the study; however, the lack of significance should be interpreted with caution considering the small sample size within these groups. The reason for numerical improvement in some subjects who received placebo in part 2 is unclear and could be related to improved adherence to concomitant therapies within the clinical-trial setting. In addition to lung function, an improvement in the respiratory symptoms domain of the CFQ-R was observed in the groups of subjects who received VX-770; this improvement exceeded the minimal clinically important difference for this domain,[13] although the improvements did not reach statistical significance. It is not known to what extent lung function can be improved in persons with cystic fibrosis in the long term and how changes in spirometric measures over the short term may reflect long-term disease progression.

The marked magnitude of the effect of VX-770 on sweat chloride concentration, as compared with the nasal potential difference and pulmonary function, may be explained by physiological differences between the sweat gland, where CFTR is involved in chloride absorption, and the airway, where CFTR is involved in chloride secretion. The variability in the end-point measures and the statistical limitations within this small study also probably contributed to the differences between outcome measures. It is not known whether there are

important interindividual differences in responses to VX-770, and the biomarker and clinical responses in large groups of subjects have not been confirmed.

We did not investigate the mechanism by which VX-770 affects the airway surface and respiratory symptoms. VX-770 is known to improve CFTR-mediated ion transport and to reduce surface liquid absorption in cultured human bronchial epithelial cells,[8] so it may have similar effects in vivo. Improvement in mucus clearance through better hydration of the airway surface could ameliorate airway obstruction by decreasing mucus plugging.

In summary, VX-770, an oral potentiator of CFTR in vitro, was associated with few severe side effects in this clinical evaluation. Some secondary end points showed no statistically significant differences versus placebo, although we observed significant within-subject improvements in respiratory (nasal potential difference) and nonrespiratory (sweat chloride concentration) biomarkers of CFTR function and improvements in lung function (spirometric assessment). The effects of VX-770 on CFTR-mediated ion transport and lung function suggest that the improvement of CFTR function may be a viable therapeutic approach in cystic fibrosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Welsh, MJ.; Ramsey, BW.; Accurso, F.; Cutting, GR. Cystic fibrosis. In: Scriver, CR.; Beaudet, AL.; Sly, WS.; Valle, D., editors. Metabolic & molecular bases of inherited disease. 8. Vol. 3. New York: McGraw-Hill; 2001. p. 5121-88.
2. Knowles M, Gatzy J, Boucher R. Relative ion permeability of normal and cystic fibrosis nasal epithelium. J Clin Invest. 1983; 71:1410–7. [PubMed: 6853720]
3. Welsh MJ. An apical-membrane chloride channel in human tracheal epithelium. Science. 1986; 232:1648–50. [PubMed: 2424085]
4. Patient registry: 2007 annual data report to the center directors. Bethesda, MD: Cystic Fibrosis Foundation; 2008.
5. Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. J Cyst Fibros. 2009; 8:91–6. [PubMed: 18952504]
6. Amaral MD, Kunzelmann K. Molecular targeting of CFTR as a therapeutic approach to cystic fibrosis. Trends Pharmacol Sci. 2007; 28:334–41. [Erratum, Trends Pharmacol Sci 2007;28:447.]. [PubMed: 17573123]
7. Yang Y, Devor DC, Engelhardt JF, et al. Molecular basis of defective anion transport in L cells expressing recombinant forms of CFTR. Hum Mol Genet. 1993; 2:1253–61. [PubMed: 7691345]
8. Van Goor F, Hadida S, Grootenhuis PD, et al. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. Proc Natl Acad Sci U S A. 2009; 106:18825–30. [PubMed: 19846789]
9. Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. J Pediatr. 2008; 153:S4–S14. [PubMed: 18639722]
10. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999; 159:179–87. [PubMed: 9872837]
11. Rowe SM, Accurso F, Clancy JP. Detection of cystic fibrosis transmembrane conductance regulator activity in early-phase clinical trials. Proc Am Thorac Soc. 2007; 4:387–98. [PubMed: 17652506]

12. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of the Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. Chest. 2005; 128:2347–54. [PubMed: 16236893]

13. Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. Chest. 2009; 135:1610–8. [PubMed: 19447923]

14. Alton EW, Stern M, Farley R, et al. Cationic lipid-mediated CFTR gene transfer to the lungs and nose of patients with cystic fibrosis: a double-blind placebo-controlled trial. Lancet. 1999; 353:947–54. [PubMed: 10459902]

15. Kerem E, Hirawat S, Armoni S, et al. Effectiveness of PTC124 treatment of cystic fibrosis caused by nonsense mutations: a prospective phase II trial. Lancet. 2008; 372:719–27. [PubMed: 18722008]

16. Konstan MW, Davis PB, Wagener JS, et al. Compacted DNA nanoparticles administered to the nasal mucosa of cystic fibrosis subjects are safe and demonstrate partial to complete cystic fibrosis transmembrane regulator reconstitution. Hum Gene Ther. 2004; 15:1255–69. [PubMed: 15684701]

17. Wilschanski M, Yahav Y, Yaacov Y, et al. Gentamicin-induced correction of CFTR function in patients with cystic fibrosis and *CFTR* stop mutations. N Engl J Med. 2003; 349:1433–41. [PubMed: 14534336]

18. Anbar RD, Lapey A, Khaw KT, et al. Does lithium carbonate affect the ion transport abnormality in cystic fibrosis? Pediatr Pulmonol. 1990; 8:82–8. [PubMed: 2352788]

19. Sermet-Gaudelus I, Renouil M, Fajac A, et al. In vitro prediction of stopcodon suppression by intravenous gentamicin in patients with cystic fibrosis: a pilot study. BMC Med. 2007; 5:5. [PubMed: 17394637]

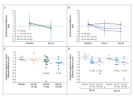

Figure 1. Measurements of the Nasal Potential Difference

Panel A shows the mean nasal potential difference (in response to the administration of a chloride-free isoproterenol solution) at baseline and day 14 during part 1 of the study in each of the four study groups. The I bars indicate the ranges, and the dashed line indicates no response. Panel B shows the mean nasal potential difference at baseline, day 14, and day 28 during part 2 of the study in each study group. The I bars indicate the ranges, and the dashed line indicates no response. Panel C shows the change in the nasal potential difference from baseline to day 14 in individual subjects (indicated by symbols) in each study group and the least-squares means (indicated by solid lines) from the mixed model in part 1 of the study. The dashed line indicates no change. Panel D shows the change in the nasal potential difference from baseline to day 14 or day 28 in individual subjects (indicated by symbols) in each study group and the medians (indicated by solid lines) in part 2 of the study. The dashed line indicates no change. P values are for within-subject comparisons.

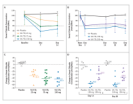

Figure 2. Measurements of Sweat Chloride Concentration

Panel A shows the mean sweat chloride concentration at baseline and days 7 and 14 during part 1 of the study for each study group. The I bars indicate the ranges. Panel B shows the mean sweat chloride concentration at baseline and days 3, 14, 21, and 28 during part 2 of the study for each study group. The I bars indicate the ranges. The dashed lines in Panels A and B indicate the lower limit of abnormal sweat chloride concentrations. Panel C shows the change in the sweat chloride concentration from baseline to day 14 in individual subjects (denoted by symbols) in each study group and the least-squares means (indicated by solid lines) from the mixed model in part 1 of the study. $P<0.001$ for all comparisons (within-subject and vs. placebo). The dashed line indicates no change. Panel D shows the change in the sweat chloride concentration from baseline to day 14 or day 28 in individual subjects (symbols) in each study group and the medians (indicated by solid lines) in part 2 of the study. At day 14, in the VX-770 150-mg group, $P = 0.02$ for within-subject comparisons and $P = 0.03$ versus placebo. In the VX-770 250-mg group, $P = 0.02$ for within-subject comparisons and $P = 0.05$ versus placebo. At day 28, in the VX-770 150-mg group, $P = 0.008$ for within-subject comparisons and $P = 0.02$ versus placebo. In the VX-770 250-mg group, $P = 0.02$ for within-subject comparisons and $P = 0.03$ versus placebo. The dashed line indicates no change.

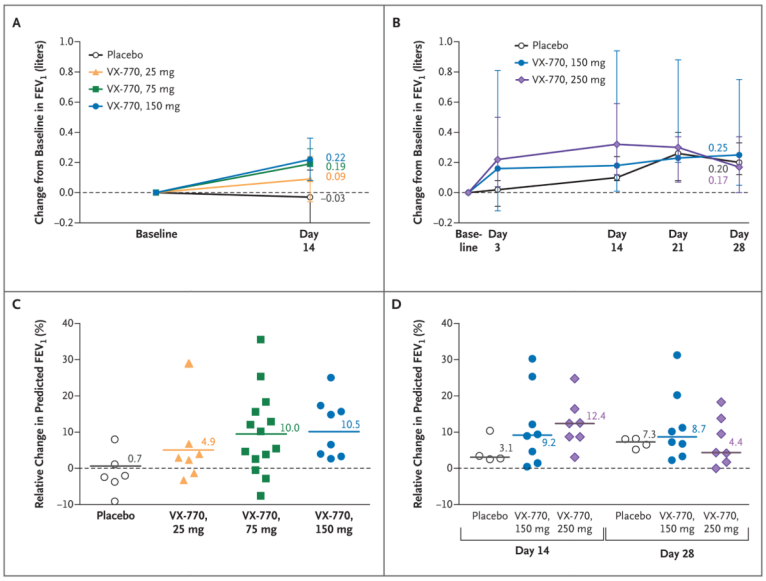

Figure 3. Measurements of Pulmonary Function

Panel A shows the mean change from baseline to day 14 in the forced expiratory volume in 1 second (FEV_1) during part 1 of the study in each study group. In the VX-770 150-mg group, P = 0.006 for within-subject comparisons and P = 0.04 versus placebo. In the VX-770 75-mg group, P = 0.003 for within-subject comparisons and P = 0.05 versus placebo. The I bars indicate the ranges. Panel B shows the median FEV_1 change from baseline during part 2 of the study in each study group. In the VX-770 250-mg group, P = 0.02 for within-subject comparisons for all time points shown except for day 28, when P = 0.03 for within-subject comparisons. In the VX-770 150-mg group, P = 0.05 for within-subject comparisons at day 3 and P = 0.008 for within-subject comparisons at days 14, 21, and 28. The I bars indicate the ranges. Panel C shows the relative change from baseline in the percentage of predicted FEV_1 from baseline to day 14 in individual subjects (indicated by symbols) in each study group and the least-squares means (indicated by solid lines) from the mixed model in part 1 of the study. In the VX-770 75-mg group, P = 0.002 for within-subject comparisons, and in the VX-770 150-mg group, P = 0.008 for within-subject comparisons. Panel D shows the relative change in the percentage of predicted FEV_1 from baseline to day 14 and day 28 in individual subjects (indicated by symbols) in each study group and the medians (indicated by solid lines) in part 2 of the study. At day 14, in the VX-770 150-mg group, P = 0.008 for within-subject comparisons. In the VX-770 250-mg group, P = 0.02 for within-subject comparisons. At day 28, in the VX-770 150-mg group, P = 0.008 for within-subject comparisons. In the VX-770 250-mg group, P = 0.03 for within-subject comparisons. In all four panels, the dashed lines indicate no change from baseline.

Table 1

Baseline Characteristics of the Subjects.*

Characteristic	Part 1†						Part 2			
	Placebo/ Placebo (N = 4)	VX-770, 25 mg/75 mg (N = 4)	VX-770, 75 mg/25 mg (N = 4)	VX-770, 75 mg/150 mg (N = 4)	VX-770, 150 mg/75 mg (N = 4)	Total (N = 20)	Placebo (N = 4)	VX-770, 150 mg (N = 8)	VX-770, 250 mg (N = 7)	Total (N = 19)
Sex — no.(%)										
Male	2 (50)	1 (25)	4 (100)	1 (25)	1 (25)	9 (45)	3 (75)	3 (38)	4 (57)	10 (53)
Female	2 (50)	3 (75)	0	3 (75)	3 (75)	11 (55)	1 (25)	5 (62)	3 (43)	9 (47)
White race — no. (%)‡	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	20 (100)	4 (100)	8 (100)	7 (100)	19 (100)
Age — yr										
Median	36	31	41	26	21	30	24	23	21	21
Range	19 to 48	22 to 51	22 to 50	19 to 34	19 to 33	19 to 51	18 to 42	18 to 40	20 to 38	18 to 42
Body-mass index										
Median	23	23	24	20	21	23	22	22	23	22
Range	22 to 29	20 to 24	19 to 27	19 to 24	17 to 26	17 to 29	21 to 23	20 to 23	20 to 25	20 to 25
CFTR genotype										
G551D/F508del	3 (75)	4 (100)	4 (100)	2 (50)	3 (75)	16 (80)	4 (100)	7 (88)	5 (71)	16 (84)
G551D/1078delT	1 (25)	—	—	—	—	1 (5)	—	—	—	—
G551D/G551D	—	—	—	—	1 (25)	1 (5)	—	—	—	—
G551D/N1303K	—	—	—	1 (25)	—	1 (5)	—	—	—	—
G551D/R553X	—	—	—	1 (25)	—	1 (5)	—	—	—	—
G551D/3849+10kbC→T	—	—	—	—	—	—	—	—	1 (14)	1 (5)
G551D/621+1G→T	—	—	—	—	—	—	—	1 (12)	—	1 (5)
G551D/G542X	—	—	—	—	—	—	—	—	1 (14)	1 (5)

Characteristic	Part 1†						Part 2			
	Placebo/ Placebo (N = 4)	VX-770, 25 mg/75 mg (N = 4)	VX-770, 75 mg/25 mg (N = 4)	VX-770, 75 mg/150 mg (N = 4)	VX-770, 150 mg/75 mg (N = 4)	Total (N = 20)	Placebo (N = 4)	VX-770, 150 mg (N = 8)	VX-770, 250 mg (N = 7)	Total (N = 19)
FEV_1										
Median % of predicted value	57	66	56	63	49	56	77	65	76	69
Range % of predicted value	48 to 97	44 to 109	42 to 65	46 to 102	42 to 58	42 to 109	53 to 112	42 to 122	40 to 106	40 to 122
40 to <70% of predicted value — no. (%)	3 (75)	3 (75)	4 (100)	2 (50)	4 (100)	16 (80)	2 (50)	5 (62)	3 (43)	10 (53)
70 to <90% of predicted value — no. (%)	—	—	—	1 (25)	—	1 (5)	—	2 (25)	3 (43)	5 (26)
≥90% of predicted value — no. (%)	1 (25)	1 (25)	—	1 (25)	—	3 (15)	2 (50)	1 (12)	1 (14)	4 (21)
Sweat chloride — mmol/liter										
Median	105.4	104.3	104.8	95.4	102.1	102.0	93.8	100.1	97.3	95.5
Range	99.0 to 112.8	60.5 to 114.5	94.3 to 115.8	93.0 to 103.3	84.0 to 104.5	60.5 to 115.8	88.0 to 109.5	86.8 to 112.5	84.8 to 115.8	84.8 to 115.8
Nasal potential difference — mV§										
Median	1.1	1.9	6.1	2.6	2.8	2.3	2.2	1.3	2.6	1.9
Range	−2.0 to 3.1	0.3 to 4.8	2.6 to 10.1	−2.1 to 4.4	1.1 to 5.0	−2.1 to 10.1	−0.3 to 3.9	−2.8 to 3.8	−1.1 to 8.0	−2.8 to 8.0
CFQ-R respiratory domain — points										
Median	NA	NA	NA	NA	NA	NA	80.6	69.4	72.2	72.2
Range							38.9 to 83.3	16.7 to 88.9	61.1 to 83.3	16.7 to 88.9

*Baseline is the median of all screening and day 1 predose values for continuous variables and the last predose value for class variables. Percentages do not always sum to 100 because of rounding. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters), CFQ-R Cystic Fibrosis Questionnaire–revised, CFTR cystic fibrosis transmembrane conductance regulator, FEV_1 forced expiratory volume in 1 second, and NA not applicable.

†In Part 1, subjects received treatment for 14 days, followed by a 7-to-28-day washout period, followed by another 14-day treatment period. Subjects who were randomly assigned to receive active drug crossed over to the other dose of VX-770 for the second treatment period (see Fig. 1 in the Supplementary Appendix).

‡Race was self-reported.

§The nasal potential difference is in response to the administration of a chloride-free isoproterenol solution.

Table 2

Moderate and Severe Adverse Events.

Event	Part 1				Part 2		
	Placebo* (N = 8)	VX-770, 25 mg (N = 8)	VX-770, 75 mg (N = 16)	VX-770, 150 mg (N = 8)	Placebo (N = 4)	VX-770, 150 mg (N = 8)	VX-770, 250 mg (N = 7)
	no. of subjects (percent)						
Upper abdominal pain							
Moderate	1 (12)	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0
Elevated blood glucose level							
Moderate	0	0	0	0	0	0	0
Severe	0	0	1 (6)	1 (12)†	0	0	0
Body aches							
Moderate	0	0	1 (6)	1 (12)‡	0	0	0
Severe	0	0	0	0	0	0	0
Catheter-related complication							
Moderate	0	0	0	1 (12)	0	0	0
Severe	0	0	0	0	0	0	0
Chronic sinusitis							
Moderate	0	0	0	0	1 (25)§	0	0
Severe	0	0	0	0	0	0	0
Cough							
Moderate	0	0	1 (6)	0	0	0	1 (14)
Severe	0	0	0	0	0	0	0
Cystic fibrosis lung¶							

Event	Part 1				Part 2		
	Placebo* (N = 8)	VX-770, 25 mg (N = 8)	VX-770, 75 mg (N = 16)	VX-770, 150 mg (N = 8)	Placebo (N = 4)	VX-770, 150 mg (N = 8)	VX-770, 250 mg (N = 7)
	no. of subjects (percent)						
Moderate	0	0	1 (6)	0	0	1 (12)	0
Severe	0	0	0	0	0	0	0
Fatigue							
Moderate	0	0	0	0	0	0	1 (14)
Severe	0	0	0	0	0	0	0
Urine positive for glucose							
Moderate	0	0	0	0	0	0	0
Severe	0	0	1 (6)	1 (12)	0	0	0
Glycosuria							
Moderate	0	0	0	1 (12)	0	0	0
Severe	0	0	0	0	0	0	0
Headache							
Moderate	1 (12)	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0
Infusion-site hemorrhage							
Moderate	0	0	0	1 (12)	0	0	0
Severe	0	0	0	0	0	0	0
Infusion-site reaction							
Moderate	0	0	0	1 (12)	0	0	0
Severe	0	0	0	0	0	0	0
Nasal discomfort							
Moderate	0	1 (12)	0	0	0	0	0

Event	Part 1				Part 2		
	Placebo* (N = 8)	VX-770, 25 mg (N = 8)	VX-770, 75 mg (N = 16)	VX-770, 150 mg (N = 8)	Placebo (N = 4)	VX-770, 150 mg (N = 8)	VX-770, 250 mg (N = 7)
	no. of subjects (percent)						
Severe	0	0	0	0	0	0	0
Nausea							
Moderate	0	0	1 (6)	1 (12)‡	0	0	0
Severe	0	0	0	0	0	0	0
Nephrolithiasis							
Moderate	0	0	1 (6)	0	0	0	0
Severe	0	0	0	0	0	0	0
Painful respiration							
Moderate	0	0	1 (6)	0	0	0	0
Severe	0	0	0	0	0	0	0
Fever							
Moderate	0	0	0	1 (12)‡	0	0	0
Severe	0	0	0	0	0	0	0
Rash							
Overall							
Moderate	0	0	1 (6)	0	0	0	0
Severe	0	0	0	0	0	0	0
Macular							
Moderate	0	0	0	0	0	0	0
Severe	0	0	0	1 (12)	0	0	0
Tension headache							

Event	Part 1				Part 2		
	Placebo* (N = 8)	VX-770, 25 mg (N = 8)	VX-770, 75 mg (N = 16)	VX-770, 150 mg (N = 8)	Placebo (N = 4)	VX-770, 150 mg (N = 8)	VX-770, 250 mg (N = 7)
	no. of subjects (percent)						
Moderate	0	0	0	0	0	0	1 (14)
Severe	0	0	0	0	0	0	0

*Subjects who received placebo in part 1 of the study were counted twice.

†One subject had elevated blood glucose levels twice during this treatment period.

‡One subject had body aches twice, fever four times, and nausea twice during this treatment period.

§One subject had chronic sinusitis twice during this treatment period.

¶This term is used in the *Medical Dictionary for Regulatory Activities* classification; it was reported by the investigator as a pulmonary exacerbation.