THE LANCET Respiratory Medicine

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Moss RB, Flume PA, Elborn JS, et al, on behalf of the VX11-770-110 (KONDUCT) Study Group. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an *Arg117His-CFTR* mutation: a double-blind, randomised controlled trial. *Lancet Respir Med* 2015; published online June 10. http://dx.doi.org/10.1016/S2213-2600(15)00201-5.

SUPPLEMENTAL MATERIALS

e-Appendix 1. Supplemental Methods

Study Design

The primary analysis for the absolute change from baseline in ppFEV$_1$ through week 24 was based on a mixed effects model for repeated measures (MMRM). The model included absolute change from baseline in percent predicted FEV$_1$ as the dependent variable, treatment (ivacaftor versus placebo), visit (weeks 2, 4, 8, 16, and 24), and treatment by visit interaction as fixed effects, and subject as a random effect, with adjustment for the continuous baseline values of age and percent predicted FEV$_1$. Visit was treated as a class variable and a compound symmetry covariance matrix was assumed to model the within-subject variability. Denominator degrees of freedom for the F-test for fixed effects were estimated using the Kenward-Roger approximation.

Three biostatisticians were involved in the randomization process: a study biostatistician blinded to the actual treatment code, an unblinded biostatistician not associated with the study, and an unblinded quality check (QC) biostatistician. The study biostatistician created the randomization specification and dummy randomization code, which was reviewed and approved by the unblinded biostatistician prior to generating the final randomization list. The unblinded QC biostatistician reviewed and approved the final randomization list. The unblinded biostatistician provided the final randomization list to the interactive voice response system (IVRS)/interactive web response system (IWRS) vendor.

Study Population

Percent predicted FEV$_1$ (ppFEV$_1$) for age, sex, and height was determined using the Hankinson standard[1] for males ≥18 years and females ≥16 years of age and the Wang standard[2] for males 6–17 years and females 6–15 years of age.

CFTR genotyping was conducted at screening (Quest Diagnostics, Valencia, CA) to confirm the genotype documented within the subject's medical record. CFTR mutations known to have a predominant channel gating defect that were excluded from the trial were *G551D, G178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P,* or *G1349D.*

Allele-specific long-range polymerase chain reaction was conducted (Arup Laboratories, Salt Lake City, UT) using an optional DNA sample to determine the *R117H* poly-T variant (5T, 7T, or 9T). For subjects whose DNA sample could not be analyzed (n=14) and for 2 subjects who did not consent to provide the optional DNA sample, the poly-T variant for the *R117H* allele was derived based on inference. Allelic phase could be derived for subjects who are homozygous for *R117H* or for poly-T variant (*ie*, 5T/5T or 7T/7T). Since the *F508del* mutation is almost exclusively associated with the 9T variant in *cis*, phase could be assigned for subjects with the *R117H/F508del* genotype and a 9T variant. Using this approach, phase could be determined for all but 2 individuals.

Assessments

Spirometry was performed according to the American Thoracic Society guidelines[3] before dosing of study medication and before administration of a bronchodilator on day 1, at weeks 2, 4, 8, 16, and 24, and at the follow-up visit.

Sweat samples were collected using an approved Macroduct® collection device (Wescor, Logan, UT) on day 1 (before dosing of study medication), at weeks 2, 4, 8, 16, and 24, and at the follow-up visit. The CFQ-R instrument was administered on day 1, at weeks 2, 4, 8, 16, and 24, and at the follow-up visit.

Subjects were asked to complete the CFQ-R in their native language, if validated translations were available.[4] The CFQ-R was administered to subjects prior to administration of study drug and any other assessment at the visit. The adult/adolescent or child versions of the CFQ-R were administered as appropriate. Reponses across all self-response questionnaire versions (eg, Adult/Adolescent and Child versions) were pooled for analysis as appropriate. Responses are provided on a 4-point Likert scale and rescaled within each domain to a score range from 0 to 100 points. Higher scores represent better health.

Pulmonary exacerbations were defined based on a modification of the criteria described by Fuchs and colleagues.[5] Pulmonary exacerbation was defined as a new or a change in antibiotic therapy (intravenous, inhaled, or oral) for any 4 or more of the following symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10%; radiographic changes indicative of pulmonary infection.

KONTINUE Study Safety Analysis

Safety data presented were SAE data reported in the Vertex Global Patient Safety Database for subjects from KONDUCT who enrolled in KONTINUE. SAEs that occurred from day 1 of KONTINUE through the cutoff date for this interim analysis (07 April 2014) were included. As of the cutoff date, most subjects (94%) had observation periods beyond 12 weeks of open label treatment.

Statistical Analyses

For all statistical analyses, baseline was defined as the most recent measurement before the first dose of study medication. The raw scores in CFQ-R were summarized into different domains of health (12 domains for subjects aged ≥14 years; 8 for the self-report version for subjects aged 12 and 13 years; 8 for the interviewer's version for subjects aged ≤11 years; and 11 for the parents/caregiver's version for subjects aged ≤13 years). Each domain was analyzed in a similar manner as for the primary outcome measure. A subject without a pulmonary exacerbation before study withdrawal was considered censored at the time of withdrawal, and a subject without a pulmonary exacerbation who completed the study was considered censored at the end of the analysis period.

Enrollment was planned for a minimum of 40 and a maximum of 80 subjects. It was estimated that a sample size of 60 subjects would provide 80% power at the 5% level of significance to detect a 6.0 percentage point difference in absolute change from baseline in $ppFEV_1$. All subjects who received study medication were included in the full-analysis and safety sets.

For the KONTINUE study interim analysis, within-group comparisons for absolute change from baseline in $ppFEV_1$ were performed using a 1-sample *t* test. All other data were summarized using summary statistics.

References

1 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(1):179-187.

2 Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG, Jr. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol.* 1993;15(2):75-88.

3 Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med.* 1995;152(3):1107-1136.

4 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(4):2347-2354.

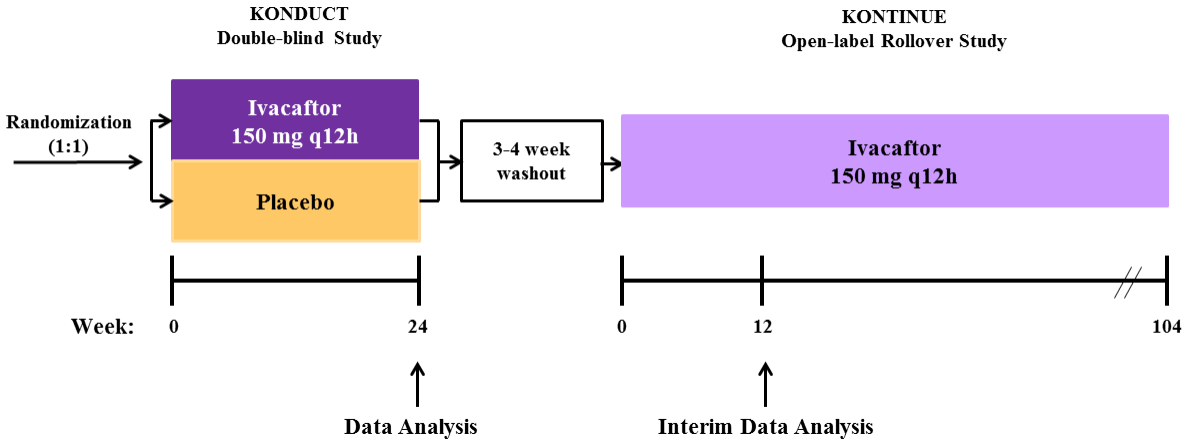
5 Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med.* 1994;331(10):637-642.

SUPPLEMENTAL TABLES AND FIGURES

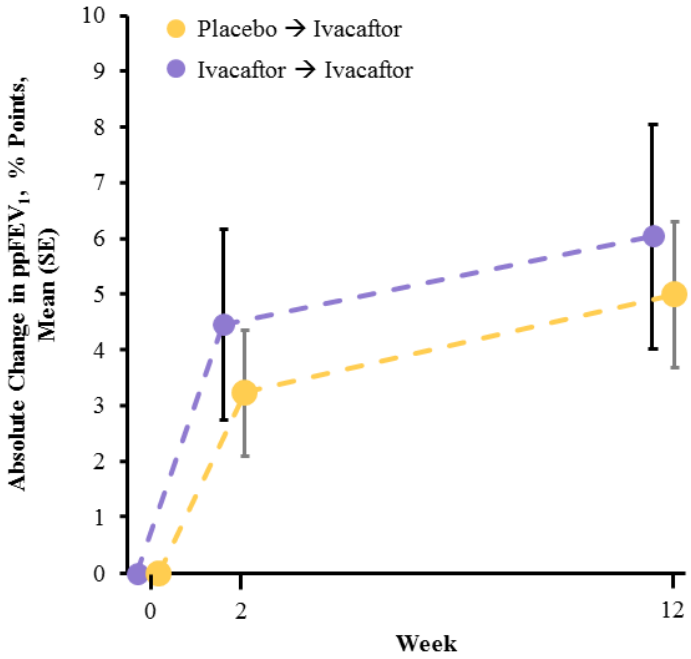
e-Table 1. **Adverse events occurring in ≥20% of subjects in any treatment group, by age**

	Age 6–11 years		Age ≥18 years	
Preferred Term, n (%)	**Placebo (n = 8)**	**Ivacaftor (n = 9)**	**Placebo (n = 26)**	**Ivacaftor (n = 24)**
Infective pulmonary exacerbation of CF	1 (13)	2 (22)	13 (50)	11 (46)
Headache	1 (13)	2 (22)	3 (12)	4 (17)
Abdominal pain	0	2 (22)	0	2 (8)
Bacterial disease carrier	0	2 (22)	1 (4)	1 (4)
Sinusitis	2 (25)	1 (11)	3 (12)	1 (4)
Cough	1 (13)	1 (11)	7 (27)	9 (38)
Sputum increased	0	0	4 (15)	5 (21)
Hemoptysis	0	0	6 (23)	0
Nasal congestion	1 (13)	0	1 (4)	5 (21)
Oropharyngeal pain	2 (25)	1 (11)	0	4 (17)
Abdominal pain upper	2 (25)	1 (11)	0	1 (4)
Pyrexia	2 (25)	1 (11)	3 (12)	1 (4)
Attention deficit/hyperactivity disorder	2 (25)	0	0	0

e-Figure 1. **Study design.**

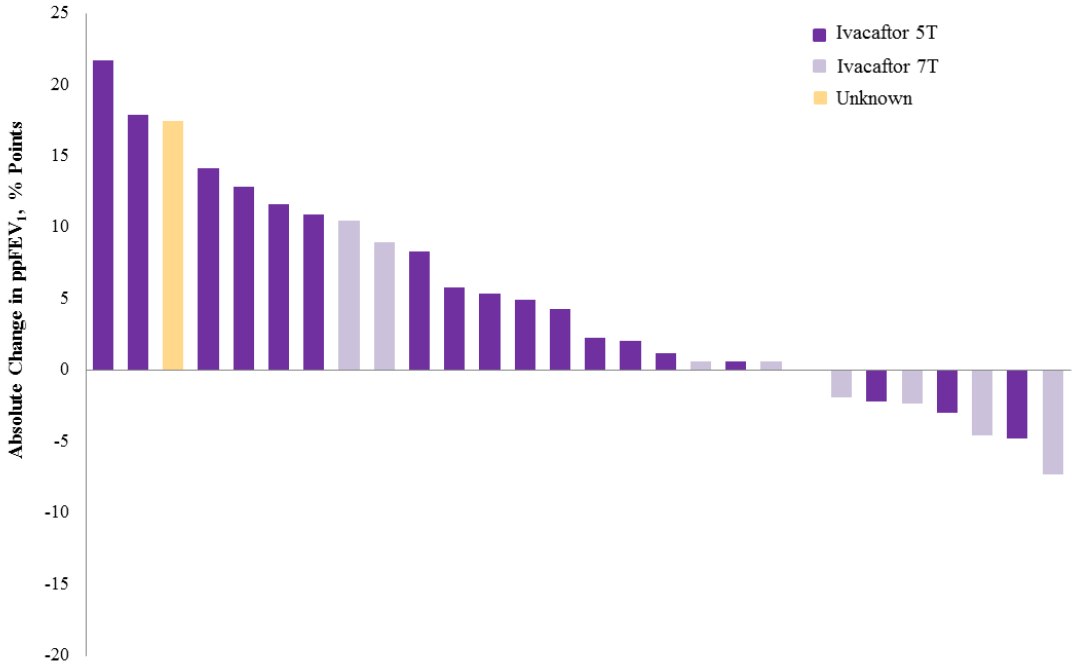


e-Figure 2. **Absolute change from postwashout baseline in percent predicted FEV_1 over 12 weeks in KONTINUE.**
ppFEV1, percent predicted forced expiratory volume in 1 second; SE, standard error.

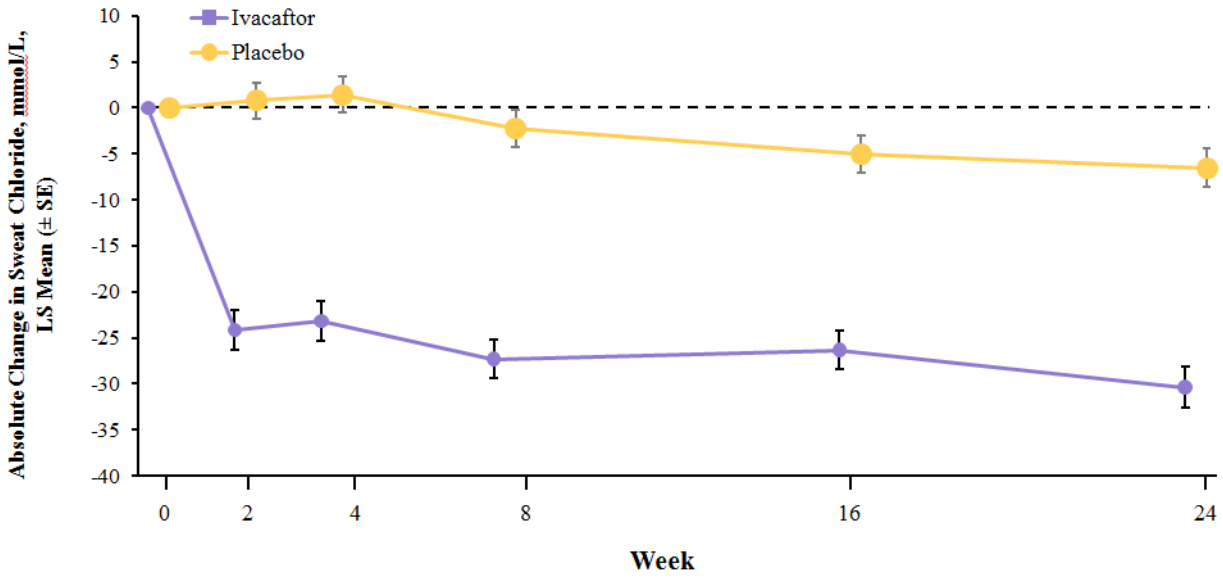


e-Figure 3. **Individual absolute change in percent predicted FEV_1 from baseline at week 24 in ivacaftor treated subjects by R117H poly-T status.**

ppFEV1, percent predicted forced expiratory volume in 1 second.

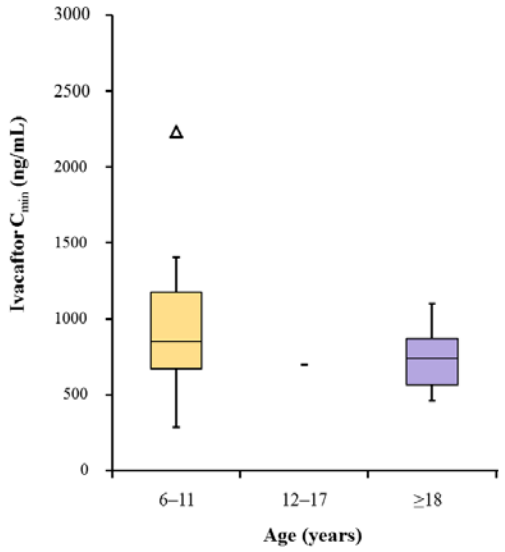


e-Figure 4. **Absolute change from baseline in sweat chloride over 24 weeks in KONDUCT (overall population).**
LS, least squares; SE, standard error.

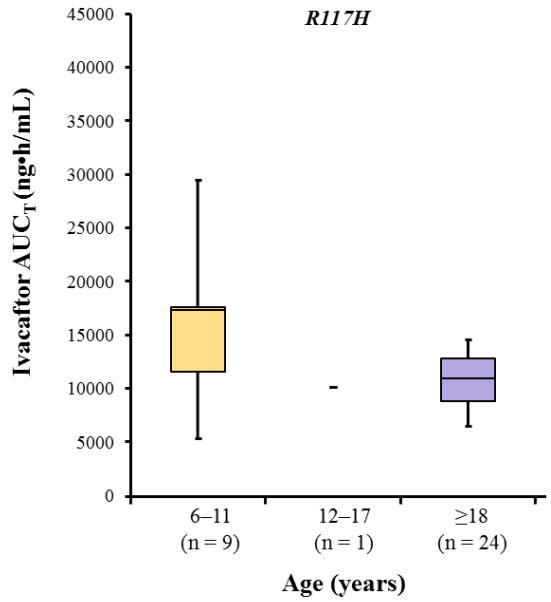


e-Figure 5. **Ivacaftor C_{min} (A) and AUC (B) by age category.**
AUC_t, area under the concentration-time curve to end of dosing period; C_{min}, minimum time to plasma clearance.

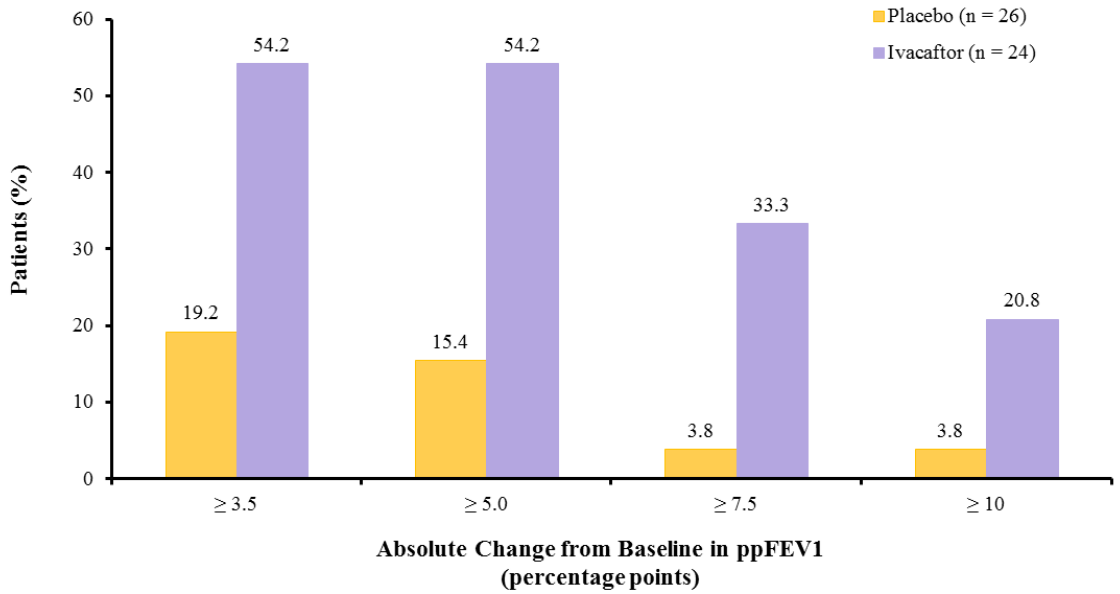
A)



B)



e-Figure 6. **Responder analysis of absolute change from baseline through week 24 in percent predicted FEV_1 (adult subjects).**
ppFEV1, percent predicted forced expiratory volume in 1 second.



e-Figure 7. **Absolute change from baseline in individual percent predicted FEV_1 responses over 24 weeks in KONDUCT and over 12 weeks in KONTINUE (children aged 6–11 years).**

[a]At baseline of KONTINUE, data presented are for KONDUCT follow-up visit.
*Subject experienced a pulmonary exacerbation coinciding with the week 16 visit. This subject completed the assigned ivacaftor treatment prior to week 24 visit because of early study closure and enrolled in KONTINUE with recovery of $ppFFEV_1$; $ppFEV_1$ value at KONTINUE baseline was 40.6%.
BL, baseline; ppFEV1, percent predicted forced expiratory volume in 1 second.