AMIKACIN LIPOSOME INHALATION SUSPENSION FOR CHRONIC *PSEUDOMONAS AERUGINOSA* INFECTION IN CYSTIC FIBROSIS

Diana Bilton, et al.

Supplementary Appendix

Table of Contents

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Selection of study population

Patients must have met all the inclusion criteria and none of the exclusion criteria to be considered eligible for randomisation into the study.

Inclusion criteria

The following inclusion criteria were applicable:

1. Written informed consent or assent obtained from the patient, parent, or legal guardian prior to the performance of any study-related procedures
2. Male or female patients ≥6 years of age (or older, if restricted by the local IRB/IEC) at screening
3. Diagnosis of CF confirmed by a positive sweat test ≥60 mEq/L or ≥60 mmol/L or by deoxyribonucleic acid analysis revealing both mutated alleles consistent with CF disease
4. History of chronic infection with *P. aeruginosa* confirmed by 3 documented positive cultures for *P. aeruginosa* within the 2 years prior to screening, with at least one obtained within 6 months prior to screening. The cultures could have been obtained from the following respiratory secretions: sputum, deep throat swabs, or bronchoalveolar lavage fluid specimens.
5. Sputum culture positive for *P. aeruginosa* at screening
6. FEV_1 ≥25% of predicted value at screening using spirometer provided by sponsor
7. SaO2 ≥90% while breathing room air at screening
8. Ability to comply with study drug use, study visits, and study procedures as judged by the Investigator
9. Ability to expectorate ≥0.4 mL of sputum
10. Willingness to have specimens stored (no genetic testing)
11. Women of childbearing potential must have had a negative result on their serum pregnancy test at screening and were willing to use reliable methods of contraception (e.g., abstinence, hormonal or barrier methods, partner sterilization, or intrauterine device) throughout the study duration. Women not of childbearing potential were defined as prepubescent, post-menopausal (i.e., amenorrhea for at least 1 year), or surgically or naturally sterile.

Exclusion criteria

The following exclusion criteria were applicable:

1. FEV_1 <25% of predicted at screening using spirometer provided by the sponsor
2. History of hypersensitivity to aminoglycosides including tobramycin solution for inhalation

3. Prior exposure to ALIS (including clinical study)
4. History of major complications of lung disease (including atelectasis, pneumothorax, major pleural effusion) within 8 weeks prior to screening
5. Haemoptysis of ≥60 mL in a 24-hour period within 4 weeks prior to screening
6. History of acute pulmonary exacerbation requiring antibiotic treatment within 4 weeks prior to screening
7. History of upper respiratory tract infection within 2 weeks prior to screening
8. Use of antipseudomonal antibiotics (IV antibiotics, inhalation antibiotics, or oral) within 4 weeks prior to Day 1
9. Radiologic finding of new pulmonary infiltrate(s) within 3 months prior to screening, or presence of other abnormalities suggesting clinically significant active pulmonary disease other than CF
10. Initiation of chronic therapy (e.g., TOBI, Colomycin®, high-dose ibuprofen, bronchodilators, inhaled anti-inflammatory agents including steroids, low-dose maintenance steroids, rhDNase, hypertonic saline, macrolides) within 4 weeks prior to Day 1
11. History of positive culture for *Burkholderia cepacia* within 2 years prior to screening
12. History of pulmonary tuberculosis or non-tuberculous mycobacterial lung disease treated within 2 years prior to screening or requiring treatment at the time of screening
13. History of allergic broncho-pulmonary aspergillosis requiring systemic steroid treatment or any other condition requiring systemic steroids at a dose ≥10 mg/day of prednisone within 3 months prior to screening
14. Presence or history of any clinically significant cardiac disease as determined by Investigator and/or, if QTc data were available, QTc prolongation >450 msec (0.450 seconds) for males or QTc >470 msec (0.470 seconds) for females or QTc prolongation >440 msec (0.440 seconds) for all patients 6-12 years of age
15. Acquired and primary immunodeficiency syndromes
16. History of hepatitis C or chronic active hepatitis B infection
17. Active pulmonary malignancy (primary or metastatic) or any malignancy requiring chemotherapy or radiation therapy within 1 year prior to screening or anticipated during the study period
18. History of biliary cirrhosis with portal hypertension
19. History of lung transplantation
20. Elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), or gamma glutamyltransferase (GGT) ≥3 × the upper limit of normal (ULN) at screening

21. Absolute neutrophils count ≤1000 at screening
22. Serum creatinine >2 × ULN at screening
23. Daily, continuous oxygen supplementation
24. Supplemental oxygen requirement of greater than 2 L/min at night
25. Administration of any investigational products within 8 weeks prior to Day 1
26. Psychotic, addictive, or other disorder limiting the ability to provide informed consent or to comply with study requirements
27. History of alcohol, medication, or illicit drug abuse within the 1 year prior to screening
28. Smoking tobacco or any substance within 6 months prior to screening or anticipated inability to refrain from smoking throughout the study
29. Positive pregnancy test or lactation at screening. All women of childbearing potential were tested for pregnancy. Women not of childbearing potential were defined as prepubescent, post-menopausal (i.e., amenorrhea for at least 1 year), or surgically or naturally sterile.
30. Any condition that, in the opinion of the Investigator, interfered with the ability to safely complete the study or adhere to study requirements

Supplementary Table 1. Reasons for study drug discontinuation (mITT Population).

Parameter	ALIS N=148	TIS N=146	All N=294
Randomised and dosed	148 (100.0)	146 (100.0)	294 (100.0)
Randomised but not dosed	0	0	0
Did the participant complete dosing at treatment cycles per protocol?			
Yes	129 (87.2)	137 (93.8)	266 (90.5)
No	19 (12.8)	9 (6.2)	28 (9.5)
Primary reason for study drug discontinuation			
Death	0	0	0
Protocol-specified safety criteria or adverse event	11 (7.4)	3 (2.1)	14 (4.8)
Persistent severe cough, study drug related	1 (0.7)	1 (0.7)	2 (0.7)
Decline predose FEV_1% predicted ≥20%, not a pulmonary exacerbation	0	0	0
Predose FEV_1% predicted <25%, not a pulmonary exacerbation	0	0	0
Creatinine >2 ULN or ×2 from baseline	0	0	0
Pregnancy	0	0	0
Adverse event	10 (6.8)	2 (1.4)	12 (4.1)
Nonadherence to study procedures	0	0	0
Withdrawal of consent	1 (0.7)	2 (1.4)	3 (1.0)

Lost to follow-up	0	0	0
Premature termination of study	0	0	0
Other	7 (4.7)	4 (2.7)	11 (3.7)

ALIS, amikacin liposome inhalation suspension; FEV_1, forced expiratory volume in 1 second; mITT, modified intention-to-treat; TIS, tobramycin inhalation solution; ULN, upper limit of normal.

Supplementary Table 2. Change from baseline in CFQ-R scales (mITT population).

Parameter[a]	Change from baseline LS mean (SE) from ANCOVA		Mean difference (ALIS–TIS)	*P* value
	ALIS (N=148)	TIS (N=146)		
Day 14				
Respiratory	4.43 (1.33)	4.35 (1.34)	0.08	.96
Body image	2.07 (1.38)	−0.46 (1.39)	2.53	.13
Digestive	2.54 (1.35)	0.12 (1.36)	2.42	.14
Eating disturbances	0.71 (1.35)	0.28 (1.37)	0.43	.79
Emotions/interrelations	2.15 (0.95)	2.62 (0.96)	−0.46	.69
Energy/well-being	1.97 (1.58)	2.79 (1.62)	−0.82	.67
Health perception	2.37 (1.56)	1.87 (1.60)	0.51	.79
Physical	1.97 (1.36)	1.02 (1.37)	0.95	.56
Role limitations	3.29 (1.19)	−2.00 (1.22)	5.29	<.01*
Social limitations	0.53 (1.17)	1.47 (1.18)	−0.93	.51
Treatment burden	3.88 (1.34)	1.00 (1.35)	2.88	.07
Day 28				
Respiratory	5.23 (1.39)	5.85 (1.42)	−0.62	.72
Body image	0.61 (1.61)	0.25 (1.64)	0.35	.86
Digestive	3.89 (1.39)	0.96 (1.42)	2.93	.08
Eating disturbances	−1.13 (1.40)	−0.32 (1.42)	−0.81	.63
Emotions/interrelations	0.42 (1.12)	1.90 (1.14)	−1.47	.28
Energy/well-being	−0.10 (1.64)	3.71 (1.68)	−3.81	.06
Health perception	−0.09 (1.53)	0.96 (1.57)	−1.05	.58
Physical	0.30 (1.48)	2.65 (1.50)	−2.36	.19
Role limitations	0.87 (1.35)	−1.72 (1.39)	2.58	.12
Social limitations	−0.95 (1.10)	1.74 (1.12)	−2.69	.05*
Treatment burden	1.27 (1.41)	−0.37 (1.43)	1.64	.34
Day 57				

Respiratory	0.90 (1.41)	3.03 (1.42)	−2.13	.22
Body image	0.47 (1.70)	−1.42 (1.72)	1.88	.37
Digestive	2.05 (1.59)	0.21 (1.59)	1.84	.34
Eating disturbances	−2.02 (1.60)	−1.44 (1.63)	−0.58	.76
Emotions/interrelations	0.60 (1.07)	−0.14 (1.09)	0.74	.57
Energy/well-being	−1.84 (1.74)	−0.36 (1.78)	−1.48	.49
Health perception	−1.64 (1.61)	−1.32 (1.65)	−0.32	.87
Physical	−2.43 (1.70)	−1.41 (1.72)	−1.02	.62
Role limitations	2.01 (1.46)	−2.02 (1.49)	4.03	.03*
Social limitations	−2.02 (1.13)	−0.37 (1.14)	−1.65	.23
Treatment burden	1.13 (1.35)	0.06 (1.36)	1.07	.51
Day 84				
Respiratory	4.25 (1.44)	3.22 (1.46)	1.03	.56
Body image	1.93 (1.71)	–2.97 (1.72)	4.89	.02*
Digestive	1.05 (1.44)	1.27 (1.45)	–0.22	.90
Eating disturbances	–0.34 (1.55)	–0.50 (1.56)	0.16	.93
Emotions/interrelations	–0.81 (1.47)	–0.65 (1.16)	–0.16	.91
Energy/well-being	–2.03 (1.77)	0.99 (1.79)	–3.01	.17
Health perception	1.44 (1.71)	–1.03 (1.72)	2.47	.24
Physical	–0.17 (1.68)	1.21 (1.70)	–1.38	.50
Role limitations	–0.31 (1.46)	–2.63 (1.47)	2.32	.20
Social limitations	–0.67 (1.22)	–1.28 (1.23)	0.61	.68
Treatment burden	1.69 (1.58)	–2.59 (1.58)	4.27	.03*
Day 113				
Respiratory	−0.27 (1.56)	1.49 (1.54)	−1.76	.35
Body image	−0.06 (1.95)	−3.15 (1.93)	3.09	.19
Digestive	2.78 (1.60)	0.42 (1.59)	2.36	.22
Eating disturbances	−1.61 (1.55)	2.14 (1.55)	−3.75	.04*
Emotions/interrelations	−1.52 (1.26)	−1.11 (1.26)	−0.42	.79

Energy/well-being	−3.24 (1.64)	−1.81 (1.64)	−1.44	.48
Health perception	−3.10 (1.77)	−2.26 (1.77)	−0.84	.70
Physical	−3.12 (1.82)	−2.27 (1.81)	−0.86	.70
Role limitations	−3.41 (1.81)	−4.83 (1.81)	1.42	.53
Social limitations	−1.43 (1.26)	0.74 (1.25)	−2.17	.16
Treatment burden	0.85 (1.51)	−0.04 (1.50)	0.89	.63
Day 140				
Respiratory	4.49 (1.36)	2.13 (1.37)	2.36	.15
Body image	−0.76 (2.03)	−1.19 (2.04)	0.44	.86
Digestive	3.20 (1.51)	1.94 (1.50)	1.26	.49
Eating disturbances	0.01 (1.40)	2.29 (1.42)	−2.28	.18
Emotions/interrelations	−1.34 (1.28)	−1.51 (1.28)	0.17	.91
Energy/well-being	−0.08 (1.70)	−0.89 (1.70)	0.82	.69
Health perception	0.43 (1.58)	−3.50 (1.58)	3.93	.04*
Physical	−0.09 (1.70)	0.68 (1.71)	−0.77	.71
Role limitations	−0.01 (1.61)	−2.70 (1.60)	2.68	.18
Social limitations	0.09 (1.23)	0.70 (1.24)	−0.61	.68
Treatment burden	0.74 (1.57)	−2.83 (1.57)	3.57	.06
Day 168				
Respiratory	2.68 (1.62)	2.74 (1.62)	−0.07	.97
Body image	−1.48 (2.05)	−2.64 (2.06)	1.15	.64
Digestive	0.24 (1.68)	-0.91 (1.68)	1.15	.57
Eating disturbances	−0.00 (1.47)	2.41 (1.48)	−2.41	.17
Emotions/interrelations	0.83 (1.14)	0.61 (1.15)	0.22	.88
Energy/well-being	−0.78 (1.82)	−1.93 (1.83)	1.15	.61
Health perception	−1.15 (1.79)	−3.20 (1.79)	2.06	.35
Physical	−2.04 (1.88)	−0.60 (1.89)	−1.45	.53
Role limitations	−4.24 (1.95)	−4.79 (1.95)	0.55	.82
Social limitations	−1.02 (1.32)	0.10 (1.33)	−1.12	.49

Treatment burden	0.09 (1.60)	−0.26 (1.61)	0.35	.86

[a] The Weight domain was not calculated at the time of data analysis. Missing values excluded.

* Statistically significant at $P \leq .05$. The ANCOVA model includes effects for treatment and the randomization strata.

ALIS, amikacin liposome inhalation suspension; ANCOVA, analysis of covariance; LS, least squares; mITT, modified intention-to-treat; CFQ-R, Cystic Fibrosis Questionnaire-Revised; TIS, tobramycin inhalation solution.

Supplementary Table 3. Relative change and adjusted change from baseline in CFQ-R Treatment Burden scale (mITT population).

Treatment Burden scale, missing values excluded	**ALIS 590 mg QD N = 148**	**TIS 300 mg BID N=146**		
Baseline[a]	n=148	n=141		
Mean (SD)	62.875 (19.2236)	61.545 (18.8055)		
Median	66.667	66.667		
Minimum, maximum	22.22, 100.00	0.00, 100.00		
Relative change from baseline, %			**Mean difference[b]**	***P* value[b]**
LS mean from ANCOVA[b]				
Day 14 (n=142; n=135)	9.69	2.73	6.96	.06
Day 28 (n=144; n=137)	4.94	2.62	2.32	.57
Day 57 (n=139; n=134)	5.18	1.75	3.43	.33
Day 84 (n=137; n=133)	6.29	−3.57	9.85	.02*
Day 113 (n=132; n=133)	4.71	4.58	0.13	.98
Day 140 (n=129; n=133)	4.18	1.49	2.69	.66
Day 168 (n=129; n=128)	3.24	1.05	2.19	.61
Adjusted change from baseline			**Mean difference[c]**	***P* value[c]**
LS mean from ANCOVA[c]				
Day 14 (n=142; n=136)	3.882	0.998	2.884	.07
Day 28 (n=144; n=138)	1.274	−0.366	1.640	.34
Day 57 (n=139; n=135)	1.132	0.059	1.072	.51
Day 84 (n=137; n=134)	1.686	−2.586	4.272	.03*
Day 113 (n=132; n=134)	0.854	−0.035	0.889	.63
Day 140 (n=129; n=134)	0.739	−2.826	3.566	.06
Day 168 (n=129; n=129)	0.094	−0.258	0.352	.86

Missing values were excluded under the assumption of missing at random, for which missing baseline or postbaseline values were excluded, but all nonmissing data were included.

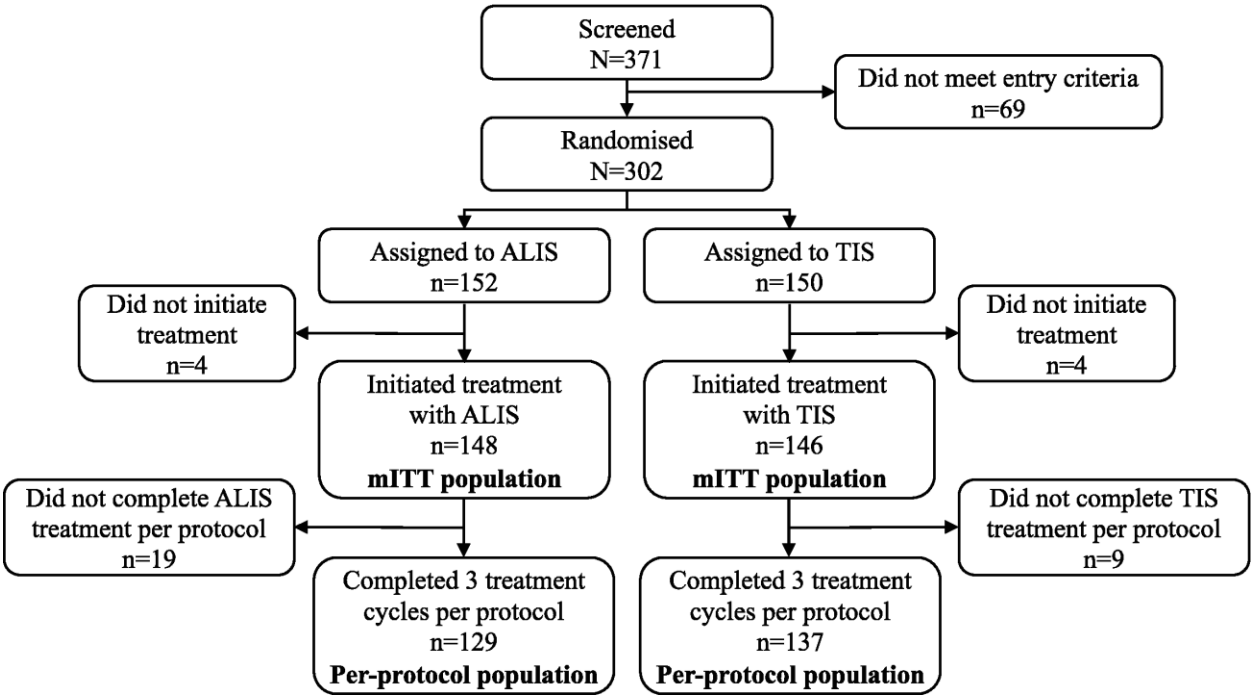
* Statistically significant at $P \leq .05$.

[a] Baseline defined as the measurement prior to and closest to the administration of the first dose of study drug.

[b] LS mean and mean difference from ANCOVA, and *P* value from treatment effect in ANCOVA model; the ANCOVA model included effects for treatment and the randomisation strata.

[c] LS mean and mean difference from ANCOVA, and *P* value from treatment effect in ANCOVA model; the ANCOVA model included effects for treatment and the randomisation strata, and used the baseline value as a covariate.

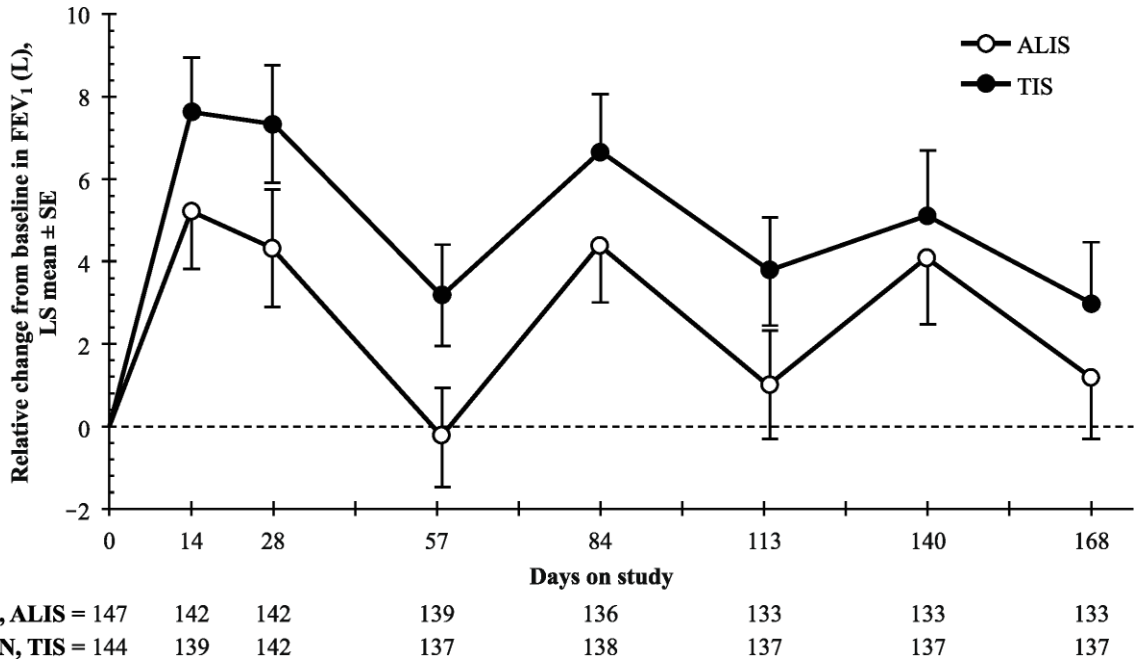
ALIS, amikacin liposome inhalation suspension; ANCOVA, analysis of covariance; BID, twice daily; CFQ-R, Cystic Fibrosis Questionnaire-Revised; LS, least squares; mITT, modified intention-to-treat; QD, once daily TIS, tobramycin inhalation solution.



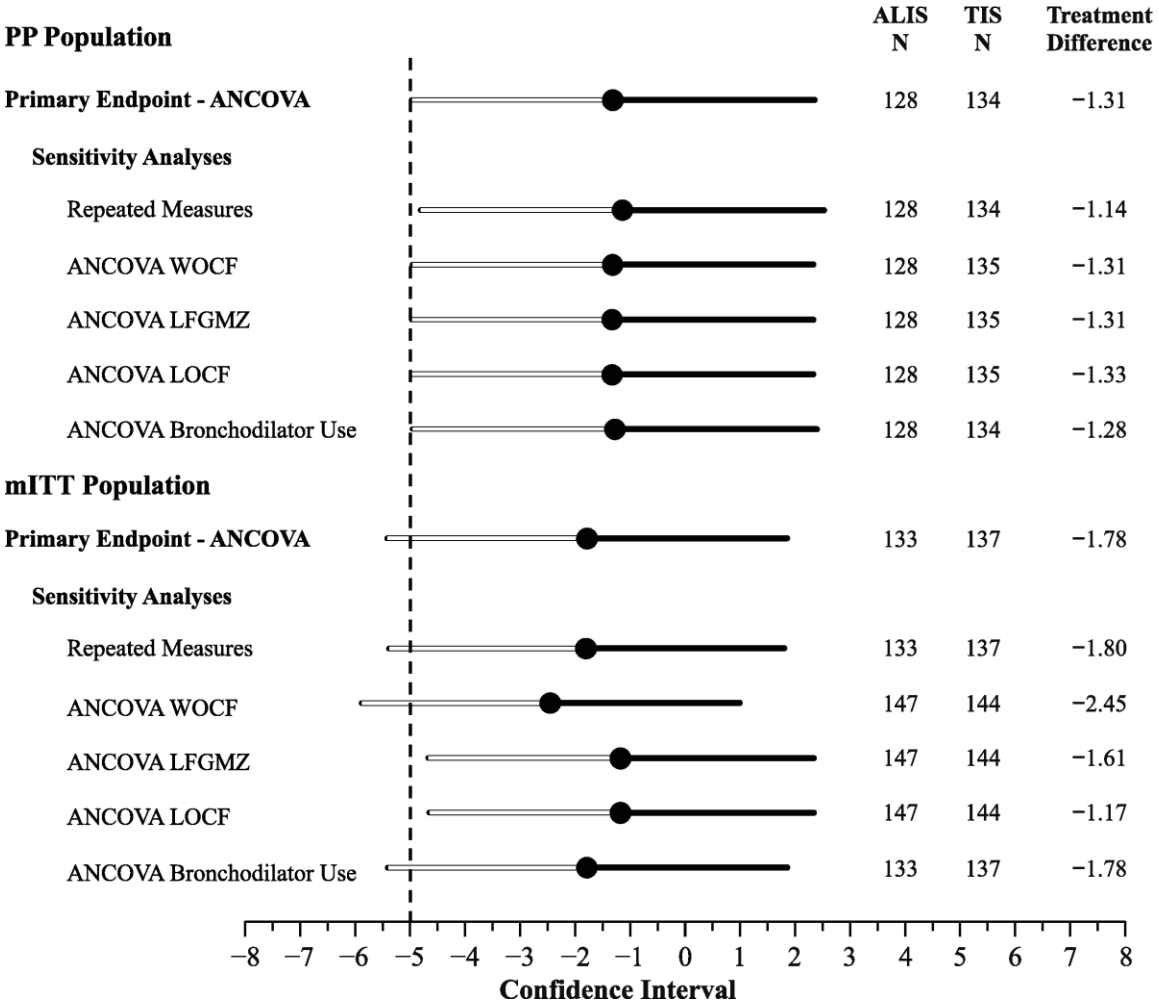
Supplementary Figure 1. Patient disposition.

The per-protocol population took ≥80% of study drug doses without missing >3 consecutive doses in any cycle, per data from the study completion electronic case report form.

ALIS, amikacin liposome inhalation suspension; mITT, modified intention-to-treat; TIS, tobramycin inhalation solution.

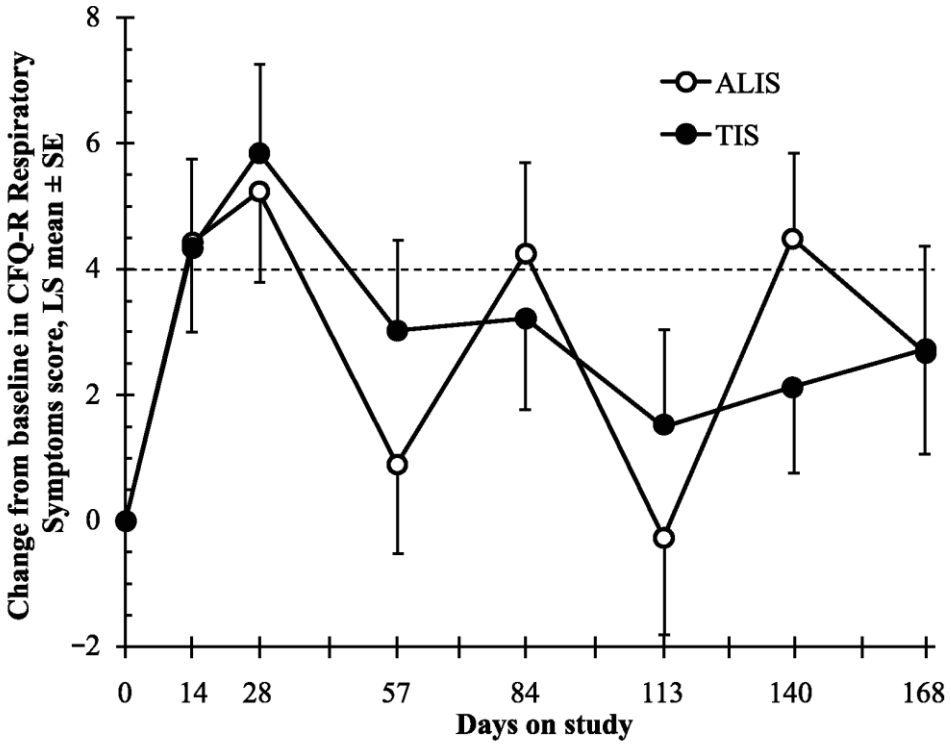


Supplementary Figure 2. Relative change from baseline in FEV_1 over time (mITT population). ALIS, amikacin liposome inhalation suspension; FEV_1, forced expiratory volume in 1 second; LS, least squares; TIS, tobramycin inhalation solution.



Supplementary Figure 3. Forest plot of treatment differences (ALIS–TIS, ± 95% CI) for the primary and sensitivity analyses of mean relative change from baseline to day 168 in FEV_1 (L) (PP and mITT populations). Vertical line represents the lower boundary of the pre-specified -5% noninferiority margin For the primary ANCOVA, the repeated measures, and ANCOVA controlling for bronchodilator use, missing values were excluded under the assumption of missing at random, for which missing baseline or postbaseline values were excluded, but all non-missing data were included.

ALIS, amikacin liposome inhalation suspension; ANCOVA, analysis of covariance; FEV_1, forced expiratory volume in 1 second; LFGMZ, last favorable group mean or zero; LOCF, last observation carried forward; LS, least squares; mITT, modified intent-to-treat; PP, per-protocol; TIS, tobramycin inhalation solution; WOCF, worst observation carried forward.



N, ALIS =	147	141	143	137	136	131	130	128
N, TIS =	142	136	138	134	135	135	135	131

Supplementary Figure 4. Change from baseline in CFQ-R Respiratory Symptoms domain (mITT population). Horizontal line represents the minimal clinically important difference ≥4) associated with the CFQ-R Respiratory Symptom domain. ALIS, amikacin liposome inhalation suspension; CFQ-R, Cystic Fibrosis Questionnaire-Revised LS, least squares; TIS, tobramycin inhalation solution.