Table 43: Clinical evidence profile: Comparison 4.1. Tobramycin versus placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Lung function: mean % change in FEV_1 % predicted (follow-up: 1 to 3 months; range of scores 1-100; Better indicated by higher values)												
4 (Galeva 2013, Konstan 2011/ EVOLVE trial, Lenoir 2007, Ramsey 1993)	randomised trials	serious[1]	serious[2]	No serious indirectness	no serious imprecision	none	257	259		MD 9.36 higher (5.01 to 13.70 higher)	LOW	CRITICAL
Number of patients with 1 or more exacerbations												
NMA outcome												CRITICAL
Suppression of the organism: eradication of the organism (negative culture) (follow-up 4 weeks)												
3 (Chuchalin 2007, Galeva 2013, Lenoir 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	71/217 (32.7%)	17/140 (12.1%)	RR 2.46 (1.20 to 5.04)	177 more per 1000 (from 24 more to 491 more)	HIGH	IMPORTANT
								14.3%		209 more per 1000 (from 92 more to 465 more)		

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Suppression of the organism: eradication of the organism (negative culture) (follow-up 6 weeks)												
1 (Lenoir 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	3/29 (10.3%)	3/30 (10%)	RR 1.03 (0.23 to 4.71)	3 more per 1000 (from 29 fewer to 578 more)	MODERATE	IMPORTANT
Suppression of the organism: eradication of the organism (negative culture) (follow-up 8 weeks)												
1 (Chuchalin 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	23/159 (14.5%)	10/83 (12%)	RR 1.2 (0.6 to 2.4)	24 more per 1000 (from 48 fewer to 169 more)	MODERATE	IMPORTANT
Suppression of the organism: eradication of the organism (negative culture) (follow-up 20 weeks)												
1 (Chuchalin 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	52/156 (33.3%)	13/79 (16.5%)	RR 2.03 (1.18 to 3.49)	169 more per 1000 (from 30 more to 410 more)	HIGH	IMPORTANT
Suppression of the organism: eradication of the organism (negative culture) (follow-up 24 weeks)												
1 (Chuchalin 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	38/159 (23.9%)	17/84 (20.2%)	RR 1.18 (0.71 to 1.96)	36 more per 1000 (from 59 fewer to 194 more)	MODERATE	IMPORTANT
Suppression of the organism: change in *P aeruginosa* sputum density log10 CFU/G (follow-up 4 weeks; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute		
1 (Galeva 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	29	26	-	MD 1.2 lower (2.03 to 0.37 lower)	MODERATE	IMPORTANT
Suppression of the organism: change in non-mucoid *P aeruginosa* sputum density log10 CFU/G (follow-up 4 weeks; Better indicated by higher values)												
1 (Konstan 2011/ EVOLVE trial)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	49	-	MD 1.76 lower (2.52 to 1 lower)	LOW	IMPORTANT
Suppression of the organism: change in mucoid *P aeruginosa* sputum density log10 CFU/G (follow-up 4 weeks; Better indicated by higher values)												
1 (Konstan 2011/ EVOLVE trial)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	49	-	MD 2.18 (2.97 to 1.39 lower)	LOW	IMPORTANT
Nutritional status: body weight change (follow-up 12 weeks; measured with: kg; Better indicated by higher values)												
1 (Lenoir 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	29	30	-	MD 0.23 higher (0.23 lower to 0.69 higher)	HIGH	IMPORTANT
Nutritional status: body weight change (follow-up 24 weeks; measured with: kg; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1 (Chuchalin 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	161	84	-	MD 0.75 higher (0.22 to 1.28 higher)	MODERATE	IMPORTANT
Minor adverse events: minor adverse events (any) (follow-up 4 weeks)												
2 (Galeva 2013, Konstan 2011/ EVOLVE trial)	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[4]	none	31/75 (41.3%)	48/75 (64%)	RR 0.66 (0.49 to 0.89)	218 fewer per 1000 (from 70 fewer to 326 more)	VERY LOW	IMPORTANT
								42.3%		144 fewer per 1000 (from 47 fewer to 216 more)		
Minor adverse events: minor adverse events (any) (follow-up 24 weeks)												
1 (Chuchalin 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	25/161 (15.5%)	13/85 (15.3 %)	RR 1.02 (0.55 to 1.88)	3 more per 1000 (from 69 fewer to 135 more)	LOW	IMPORTANT
Minor adverse events: auditory impairment (follow-up 4 weeks)												
1 (Galeva 2013)	randomised trials	no serious risk	no serious inconsistency	no serious indirectness	very serious[7]	none	3/29 (10.3%)	2/26 (7.7%)	RR 1.34 (0.24 to 7.43)	26 more per 1000 (from 58 fewer to 495 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
		of bias										
Minor adverse events: auditory impairment (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/152 (0%)	0/148 (0%)	-	-	HIGH	IMPORTANT
Minor adverse events: auditory impairment (follow-up 42 weeks)												
1 (Ramsey 1993)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/36 (0%)	0/35 (0%)	-	-	HIGH	IMPORTANT
Minor adverse events: cough (follow-up 4 weeks)												
2 (Galeva 2013, Konstan 2011/ EVOLVE trial)	randomised trials	very serious[6]	very serious[8]	no serious indirectness	very serious[7]	none	11/75 (14.7%)	13/75 (17.3 %)	RR 1.67 (0.08 to 36.11)	116 more per 1000 (from 159 fewer to 1000 more)	VERY LOW	IMPORTANT
								-		-		
Minor adverse events: tinnitus (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[4]	none	8/258 (3.1%)	0/262 (0%)	RR 17.26 (1 to	-	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute		
		risk of bias							297.54)			
Minor adverse events: headaches (follow-up 4 weeks)												
1 (Konstan 2011/ EVOLVE trial)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/46 (2.2%)	1/49 (2%)	RR 0.36 (0.04 to 3.29)	13 fewer per 1000 (from 20 fewer to 47 more)	VERY LOW	IMPORTANT
Major adverse events: any (follow-up 4 weeks)												
2 (Galeva 2013, Konstan 2011/ EVOLVE trial)	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	4/75 (5.3%)	8/75 (10.7%)	RR 0.52 (0.16 to 1.64)	51 fewer per 1000 (from 90 fewer to 68 more)	VERY LOW	IMPORTANT
								3.9%		19 fewer per 1000 (from 33 fewer to 25 more)		
Major adverse events: any (follow-up 24 weeks)												
1 (Chuchalin 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/161 (10.6%)	22/85 (25.9%)	RR 0.41 (0.23 to 0.73)	153 fewer per 1000 (from 70 fewer to 199 fewer)	HIGH	IMPORTANT
Major adverse events: haemoptysis (follow-up 4 weeks)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1 (Konstan 2011/ EVOLVE trial)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/46 (2.2%)	1/49 (2%)	RR 1.07 (0.07 to 16.54)	1 more per 1000 (from 19 fewer to 317 more)	VERY LOW	IMPORTANT
Major adverse events: haemoptysis (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	69/258 (26.7%)	81/262 (30.9 %)	RR 0.87 (0.66 to 1.13)	40 fewer per 1000 (from 105 fewer to 40 more)	MODERATE	IMPORTANT
Major adverse events: pneumothorax (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	1/258 (0.39%)	4/262 (1.5%)	RR 0.25 (0.03 to 2.26)	11 fewer per 1000 (from 15 fewer to 19 more)	LOW	IMPORTANT
Mortality (follow-up 4 weeks)												
1 (Konstan 2011/ EVOLVE trial)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	0/46 (0%)	1/49 (2%)	RR 0.35 (0.01 to 8.49)	13 fewer per 1000 (from 20 fewer to 153 more)	LOW	IMPORTANT
Mortality (follow-up 3 to 12 months)												
2 (Chuchalin 2007,	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[3]	none	1/419 (0.24%)	6/348 (1.7%)	RR 0.17 (0.03	14 fewer per 1000 (from 17	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Ramsey 1999)		risk of bias							to 1.09)	fewer to 2 more)		
Emergence of resistant organisms: frequency of Tobramycin-resistant *P aeruginosa* (follow-up 24 weeks)												
2 (Chuchalin 2007, Ramsey 1999)	randomised trials	no serious risk of bias	very serious[10]	no serious indirectness	serious[4]	none	86/376 (22.9%)	31/296 (10.5%)	RR 1.95 (0.86 to 4.42)	99 more per 1000 (from 15 fewer to 385 more)	VERY LOW	IMPORTANT
Emergence of resistant organisms: frequency of new isolates of drug resistant *B cepacia* (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/258 (0%)	0/262 (0%)	-	-	HIGH	IMPORTANT
Emergence of resistant organisms: frequency of new isolates of drug resistant *S maltophilia* (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	3/258 (1.2%)	1/262 (0.38%)	RR 3.05 (0.32 to 29.1)	8 more per 1000 (from 3 fewer to 107 more)	LOW	IMPORTANT
Emergence of resistant organisms: frequency of new isolates of drug resistant *A xylosidans* (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious risk	no serious inconsistency	no serious indirectness	very serious[7]	none	1/258 (0.39%)	1/262 (0.38%)	RR 1.02 (0.06 to 16.15)	0 more per 1000 (from 4 fewer to 58 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tobramycin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
		of bias										
Emergence of resistant organisms: frequency of new isolates of drug resistant *aspergillus* (follow-up 24 weeks)												
1 (Ramsey 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/196 (2%)	20/193 (10.4%)	RR 0.2 (0.07 to 0.57)	83 fewer per 1000 (from 45 fewer to 96 fewer)	HIGH	CRITICAL

Abbreviations: CFU/G: colony forming units per gram; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; kg: kilogrammes; MD: mean difference; RR: risk ratio
1 The quality of the evidence was downgraded by 1, as 1 of the trials had unclear risk of bias for the domains randomisation, allocation concealment, and blinding and another trial had unclear risk of bias for the domains randomisation, allocation concealment and high risk of bias for blinding
2 The quality of the evidence was downgraded by 1 due to moderate inconsistency (I2=51%). Sub-group analysis was not conducted, as all of the trials showed a beneficial effect of tobramycin
3 The quality of the evidence was downgraded by 1 as the 95% CI crossed the null effect
4 The quality of the evidence was downgraded by 1 as the 95% CI crossed 1 default MID
5 The quality of the evidence was downgraded by 2 due to unclear risk of bias for the domains randomisation, allocation concealment and high risk of bias for blinding
6 The quality of the evidence was downgraded by 2, as the largest trial had unclear risk of bias for the domains randomisation, allocation concealment and high risk of bias for blinding
7 The quality of the evidence was downgraded by 2 as the 95% CI crossed 2 default MIDs
8 The quality of the evidence was downgraded by 2 due to very serious inconsistency (I2=77%).
9 The quality of the evidence was downgraded by 2 as the 95% CI is very wide and it crossed the null effect. The study is underpowered to detect differences
10 The quality of the evidence was downgraded by 2 due to very serious inconsistency (I2=79%)