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Year in review: Bronchiectasis

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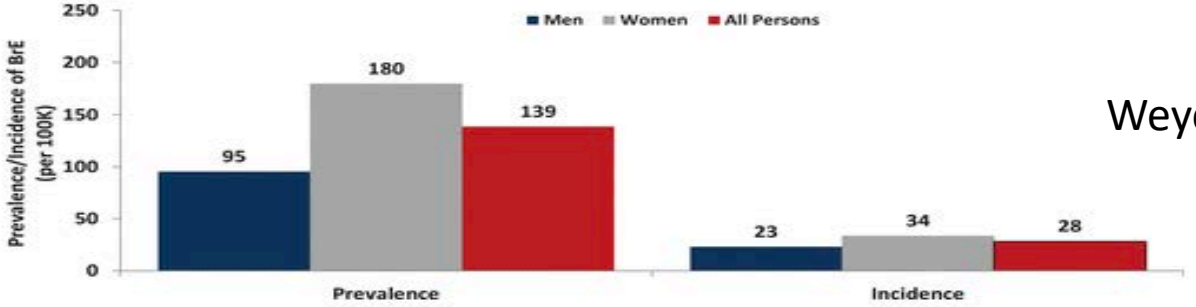
Disclosure

- I consult for Savara Pharmaceuticals
  - Inhaled GM-CSF, inhaled vancomycin, inhaled amikacin-Fosfomycin

Bronchiectasis is finally getting the attention of drug companies and regulatory authorities

US Healthcare Claims Data 2013



Weycker et al Chron Respir Dis 2017

Figure 1. Prevalence and incidence (annual) of bronchiectasis among US adults, overall and by sex.

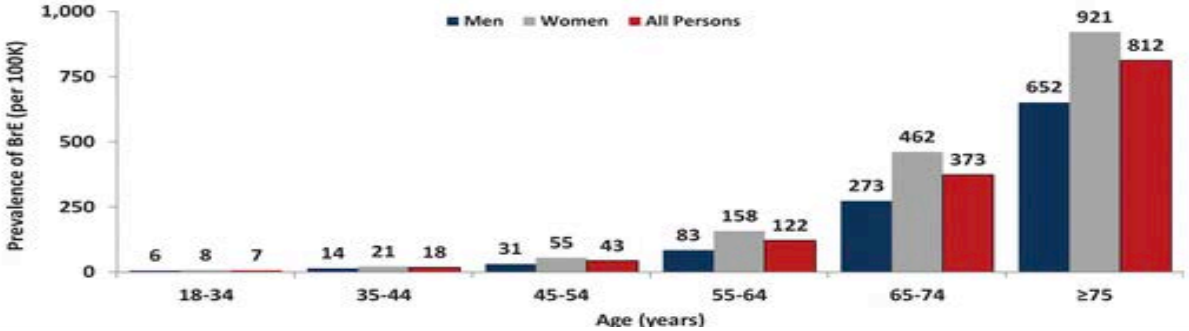


TABLE 3

Total cost of bronchiectasis and costs separated by main cost types compared with matched control patients after adjusting for age, sex and Charlson Comorbidity Index scores

	Control group without bronchiectasis[¶¶]		Incident bronchiectasis patients[++]		Ratio of the mean (95% CI)	p-value[§§]
	Sum	Mean[ƒƒ] (95% CI)	Sum	Mean[ƒƒ] (95% CI)		
Outpatient diagnostic and visiting costs[#]	1840235.71	2792.47 (2699.33–2885.61)	632567.17	2983.81 (2795.81–3171.81)	1.07 (0.995–1.15)	0.27[NS]
Costs of remedies[¶,+]	158094.73	239.9 (215.44–264.36)	82556.87	389.42 (301.68–477.16)	1.62 (1.27–2.08)	0.02
Medical aids costs[¶,§]	259848.97	394.31 (300.36–488.26)	230186.30	1085.78 (809.87–1361.69)	2.75 (1.95–3.90)	<0.001
Costs of antibiotics[##]	56891.69	85.31 (77.80–92.82)	87727.50	413.81 (176.28–651.34)	4.85 (2.72–6.84)	<0.001
Costs of mucoactive agents	9322.73	14.15 (10.51–16.79)	14863.81	70.11 (51.65–88.57)	4.96 (4.91–5.28)	0.001
Total cost	9382176.66	14236.99 (11318.87–17155.21)	3950529.29	18634.57 (15891.02–23871.13)	1.31 (1.02–1.68)	<0.001

38.5 million Euro per year in direct and indirect costs to the German Healthcare system

Data are presented as EUR, unless otherwise stated. #: outpatient costs comprise reimbursement for outpatient physician's office visits, laboratory diagnostics and imaging; ¶: as outpatients; +: remedies comprise physiotherapy treatments and modalities such as active cycle of breathing and postural drainage techniques; §: medical aids comprise nebulisers and respiration therapy equipment; ƒ: sick pay is paid out in the statutory company health insurance as a substitute wage from day 43 of the sick leave according to Section 44 of the 5th German Social Code (SGB V; www.sozialgesetzbuch-sgb.de); ##: prescribed pharmaceuticals according to German national drug (Anatomical Therapeutic Chemical) codes; ¶¶: n=685; ++: n=231; §§: Wilcoxon–Mann–Whitney test (two-sided); ƒƒ: adjusted to patients who died during the observation period. NS: nonsignificant.

Diel et al ERJ 2019

Treatment studies – the “good” the “bad” and the “ugly”

Question 1

- Concerning bronchiectasis
- A – Phase III randomised controlled trials have shown that inhaled antibiotics improve outcomes
- B – Phase III randomised controlled trials have shown that oral macrolides improve outcomes
- C – A and B are correct
- D – Neither A and B are correct

Question 1

- Concerning bronchiectasis
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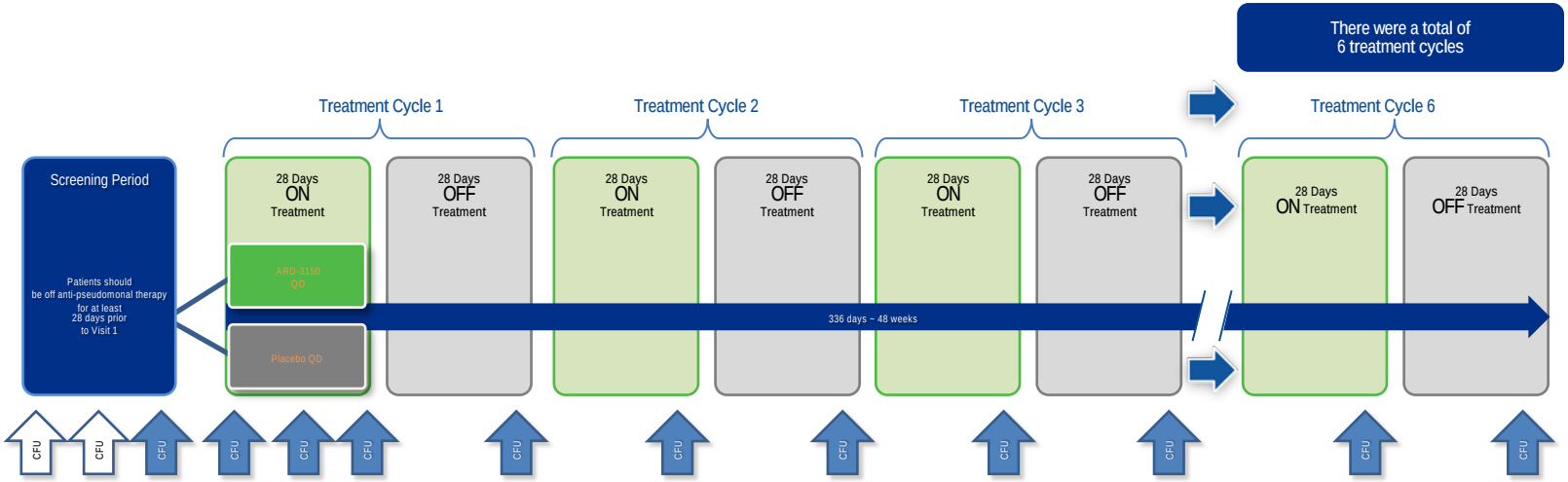
- B – Phase III randomised controlled trials have shown that oral macrolides improve outcomes
- C – A and B are correct
- D – Neither A and B are correct

Failed phase III trials of inhaled antibiotics

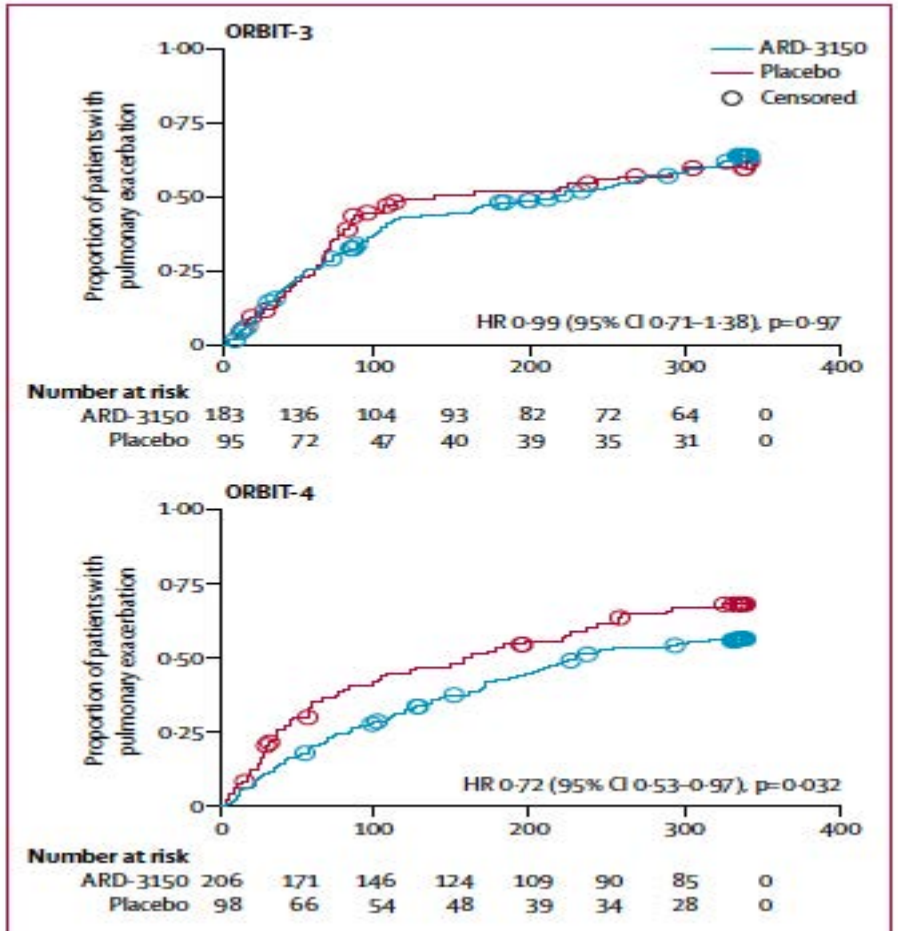
- DPI cipfloxacin (RESPIRE 1 and RESPIRE 2)
  - Bayer
- Nebulised liposomal ciprofloxacin (ORBIT-3, ORBIT-4)
  - Aradigm
- Nebulized aztreonam (AIR-BX1, AIR-BX2)
  - Gilead

Study Design – ORBIT-3 and ORBIT-4

Nebulized ARD-3150 or placebo were administered once daily for 6 cycles of 28 days on treatment, separated by 28 days off treatment, during the 48-week double-blind phase



Haworth et al Respiratory Med 2019



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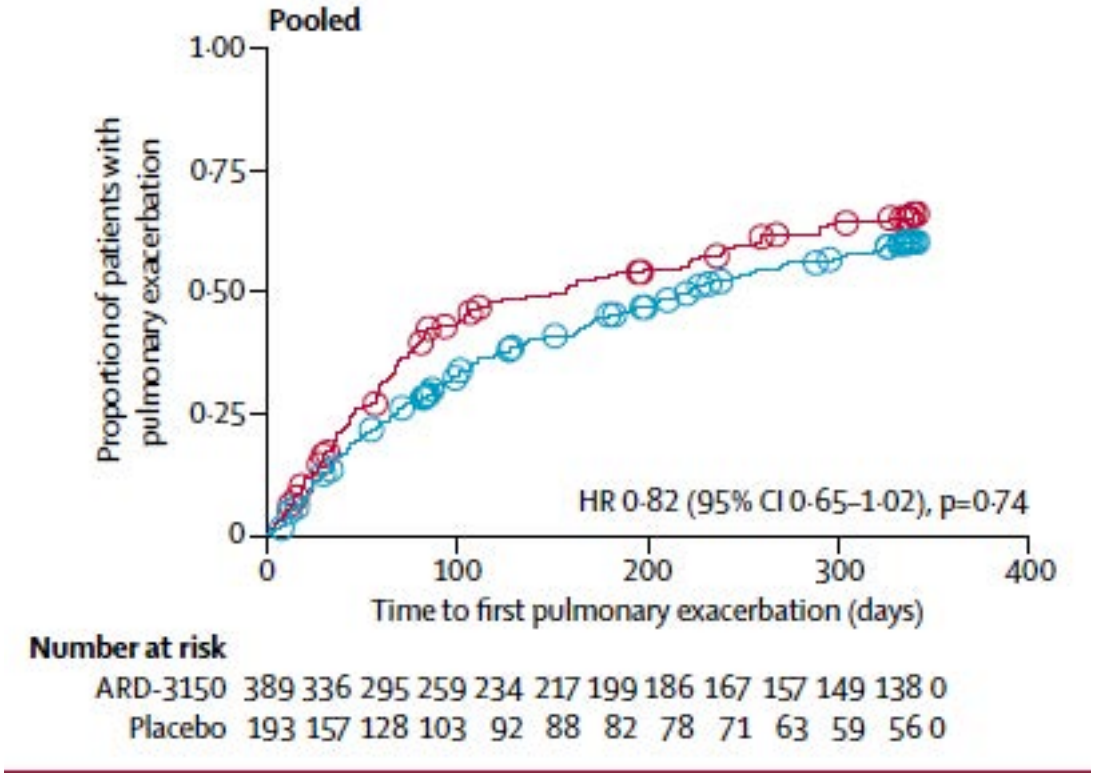
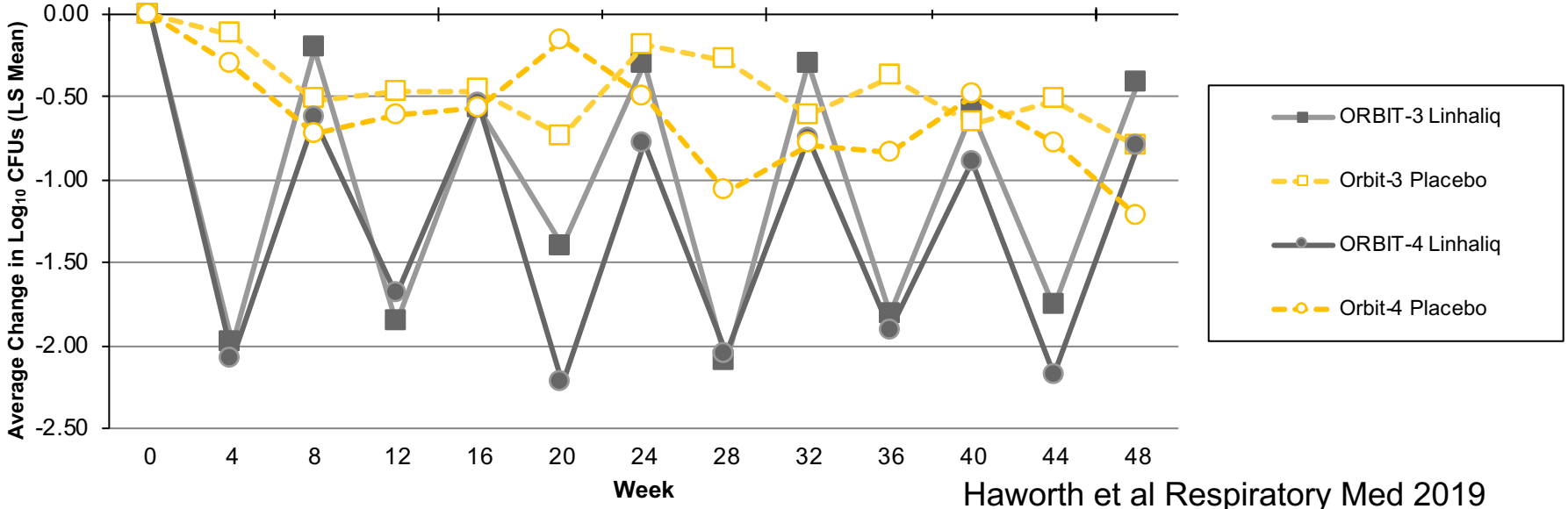


Haworth et al Respiratory Med 2019

Inhaled Cipro effectively cleared bacteria



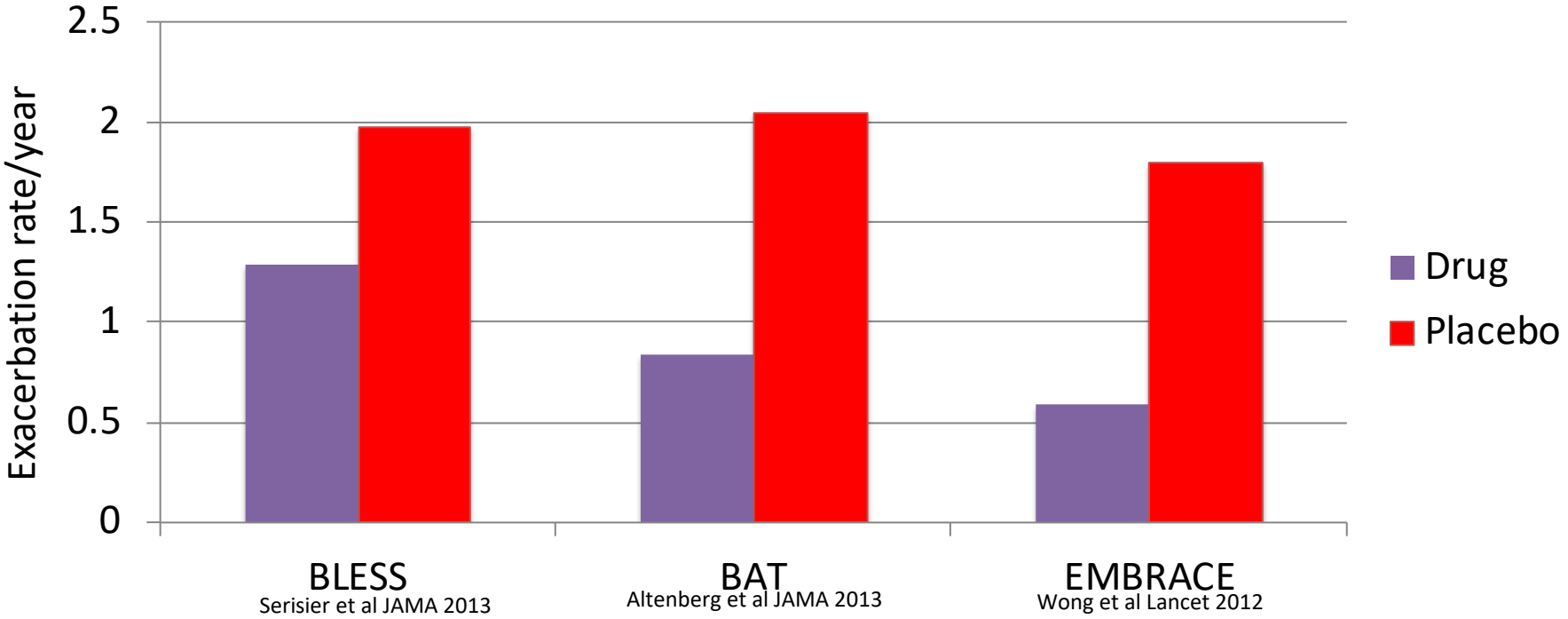
Haworth et al Respiratory Med 2019

Subgroup analyses based on prior exacerbation frequency

Study	Exacerbation frequency	Linhaliq, n	Placebo, n	RR	95% CI
ORBIT4	2-3	166	76	0.68	0.50-0.93
ORBIT4	4+	40	21	0.52	0.31-0.87
ORBIT3	2-3	141	69	0.94	0.66-1.32
ORBIT3	4+	42	25	0.68	0.44-1.04

Haworth et al Respiratory Med 2019

3 Macrolide RCT's



Macrolides

- BLESS
  - Serisier et al JAMA 2013
  - Erythromycin 400mg bd in 117pts for 12/12

- BAT
  - Altenberg et al JAMA 2013
  - Azithromycin 250mg daily in 83 pts for 12/12

- EMBRACE
  - Wong et al Lancet 2012
  - Azithromycin 500mg 3x/week in 141 patients for 6/12

Question 2

- Which of these macrolides inhibits cytochrome P450?
- A – Clarithomycin
- B – Azithromycin
- C – Erythromcin
- D – A and B but not C
- E – A and C but not B
- F – B and C but not A

Question 2

- Which of these macrolides inhibits cytochrome P450?
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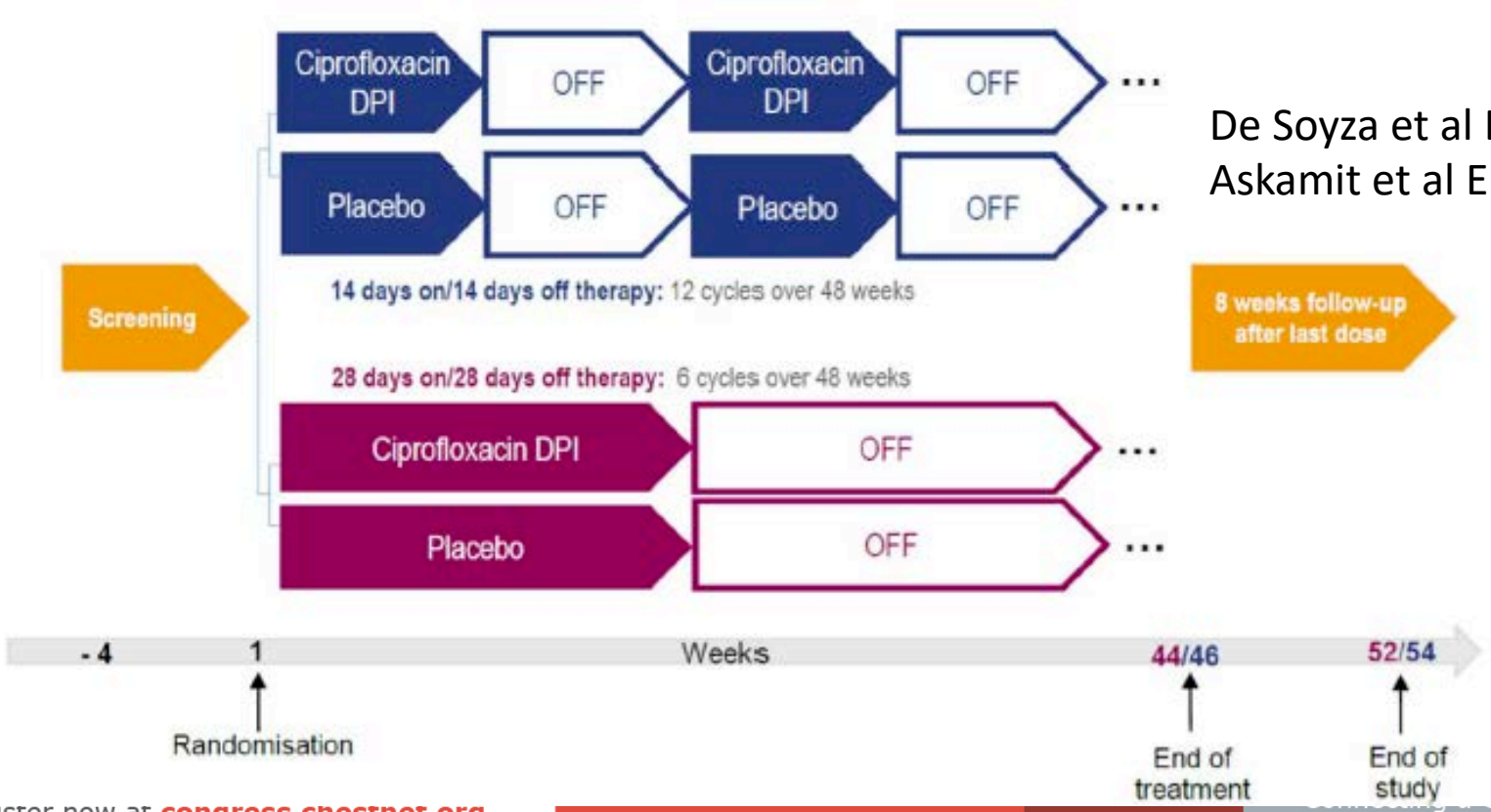
Macrolide use was not stratified at baseline in the ORBIT studies

Macrolide imbalance at randomization

Trial	Group		Macrolide use at randomization n (%)
ORBIT-3 Overall Population	Ciprofloxacin DI	(n=183 patients)	43 (23%)
	Placebo	(n=95 patients)	13 (14%)
ORBIT-4 Overall Population	Ciprofloxacin DI	(n=206 patients)	34 (17%)
	Placebo	(n=98 patients)	24 (24%)

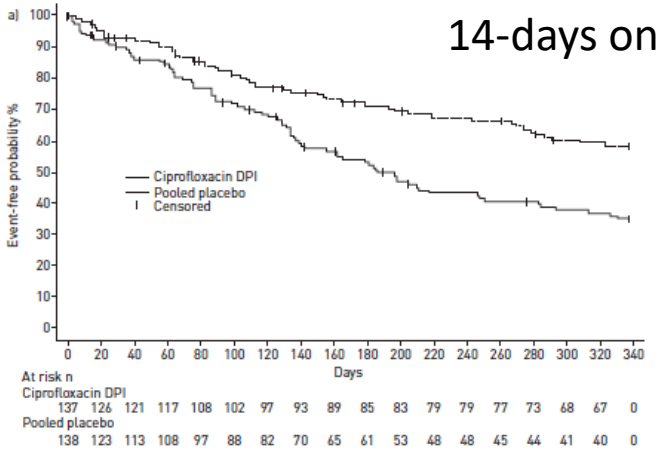
Haworth et al Respiratory Med 2019

RESPIRE 1 and RESPIRE 2

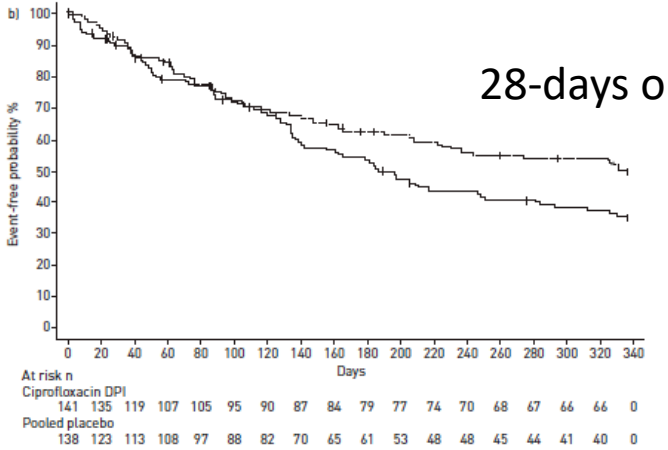


De Soyza et al ERJ 2018
Askamit et al ERJ 2018

14-days on-off



28-days on-off

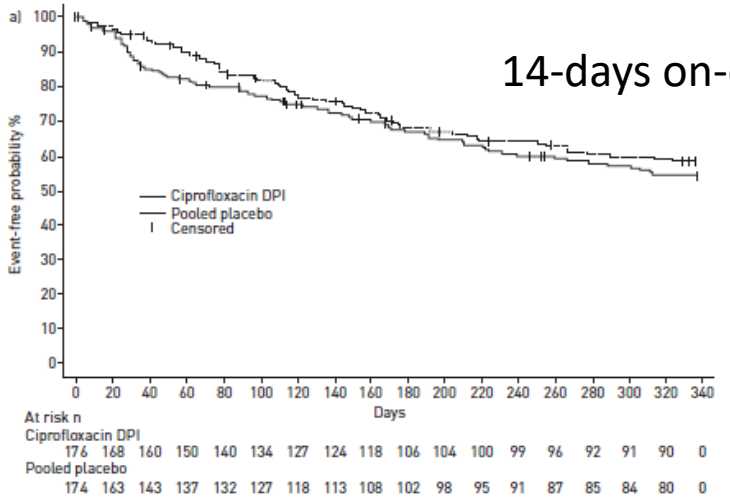


Respire 1
De Soyza et al ERJ 2018

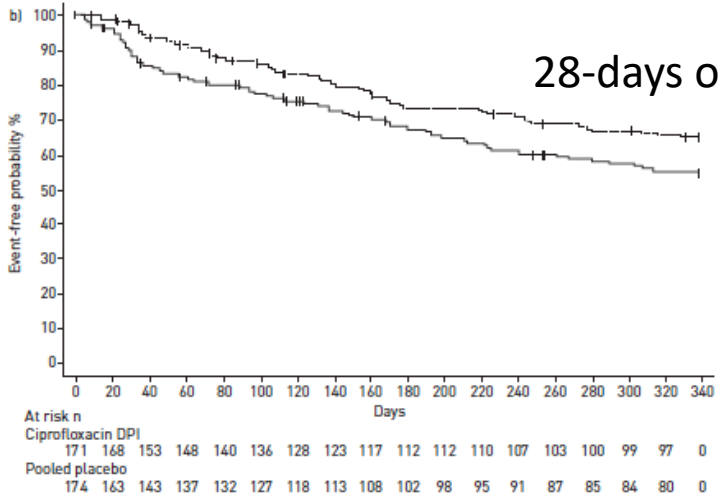
TABLE 3 Primary end-points: time to first exacerbation and frequency of exacerbations[#] in patients treated with ciprofloxacin dry powder for inhalation (DPI) *versus* placebo over 48 weeks

	HR or IRR[¶] (97.5% CI)	p-value (Wald-type test)
Time to first exacerbation[¶]		
Ciprofloxacin DPI 14 days on/off *versus* pooled placebo	0.53 (0.36–0.80)	0.0005
Ciprofloxacin DPI 28 days on/off *versus* pooled placebo	0.73 (0.50–1.07)	0.0650
Frequency of exacerbations[¶]		
Ciprofloxacin DPI 14 days on/off *versus* matching placebo	0.61 (0.40–0.91)	0.0061
Ciprofloxacin DPI 28 days on/off *versus* matching placebo	0.98 (0.64–1.48)	0.8946

14-days on-off



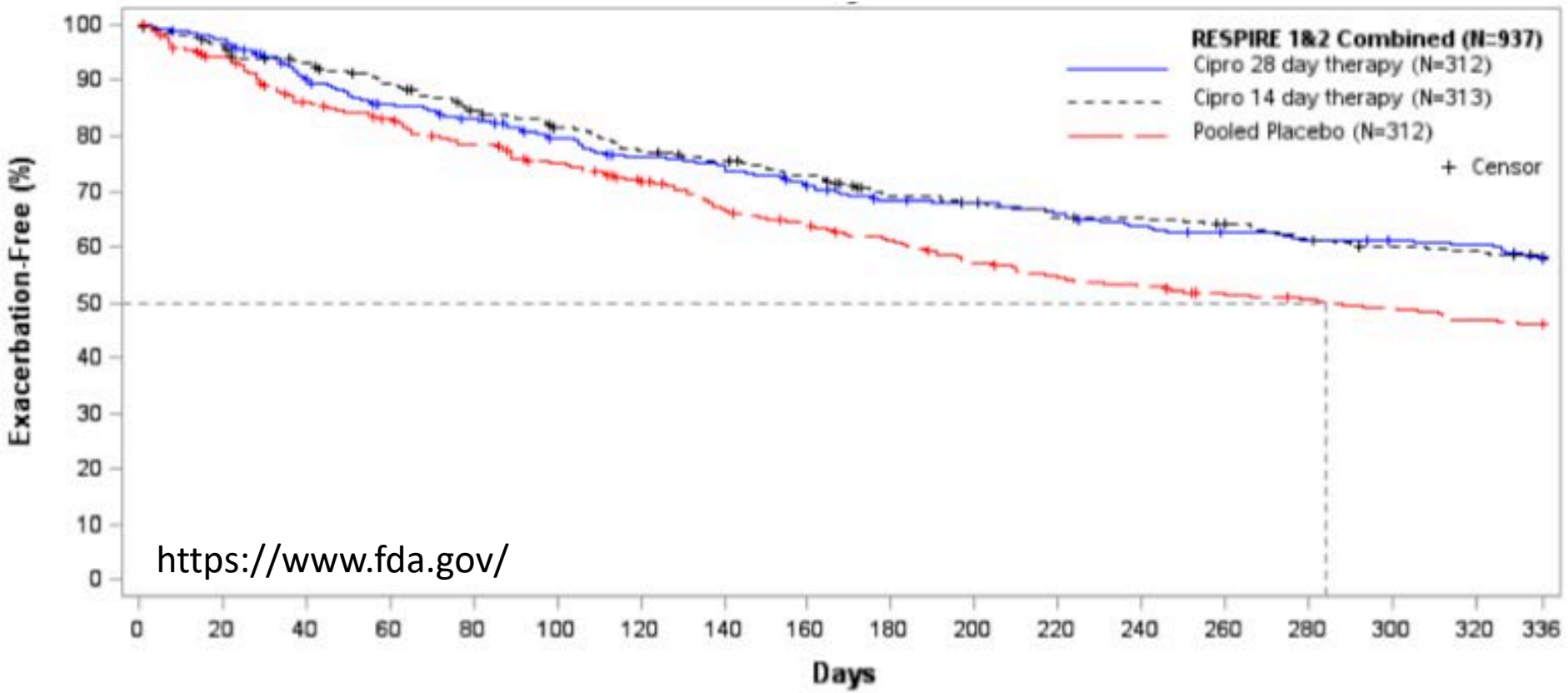
28-days on-off



Respire 2
Askamit et al ERJ 2018

TABLE 3 Primary end-points: time to first exacerbation and frequency of exacerbations[#] in patients treated with ciprofloxacin dry powder for inhalation (DPI) *versus* placebo over 48 weeks

Primary end-point	HR or IRR[¶] (95.1% or 99.9% CI[+])	p-value (Wald-type test)
Time to first exacerbation		
Ciprofloxacin DPI 14 days on/off *versus* pooled placebo	0.8662 (0.62–1.21)	0.3965
Ciprofloxacin DPI 28 days on/off *versus* pooled placebo	0.7062 (0.39–1.27)	0.0511
Frequency of exacerbations		
Ciprofloxacin DPI 14 days on/off *versus* matching placebo	0.8313 (0.59–1.17)	0.2862
Ciprofloxacin DPI 28 days on/off *versus* matching placebo	0.5493 (0.30–1.02)	0.0014



'Exacerbations defined as exacerbations with systemic antibiotic use,fever or malaise/fatigue and worsening of at least three signs/symptoms'

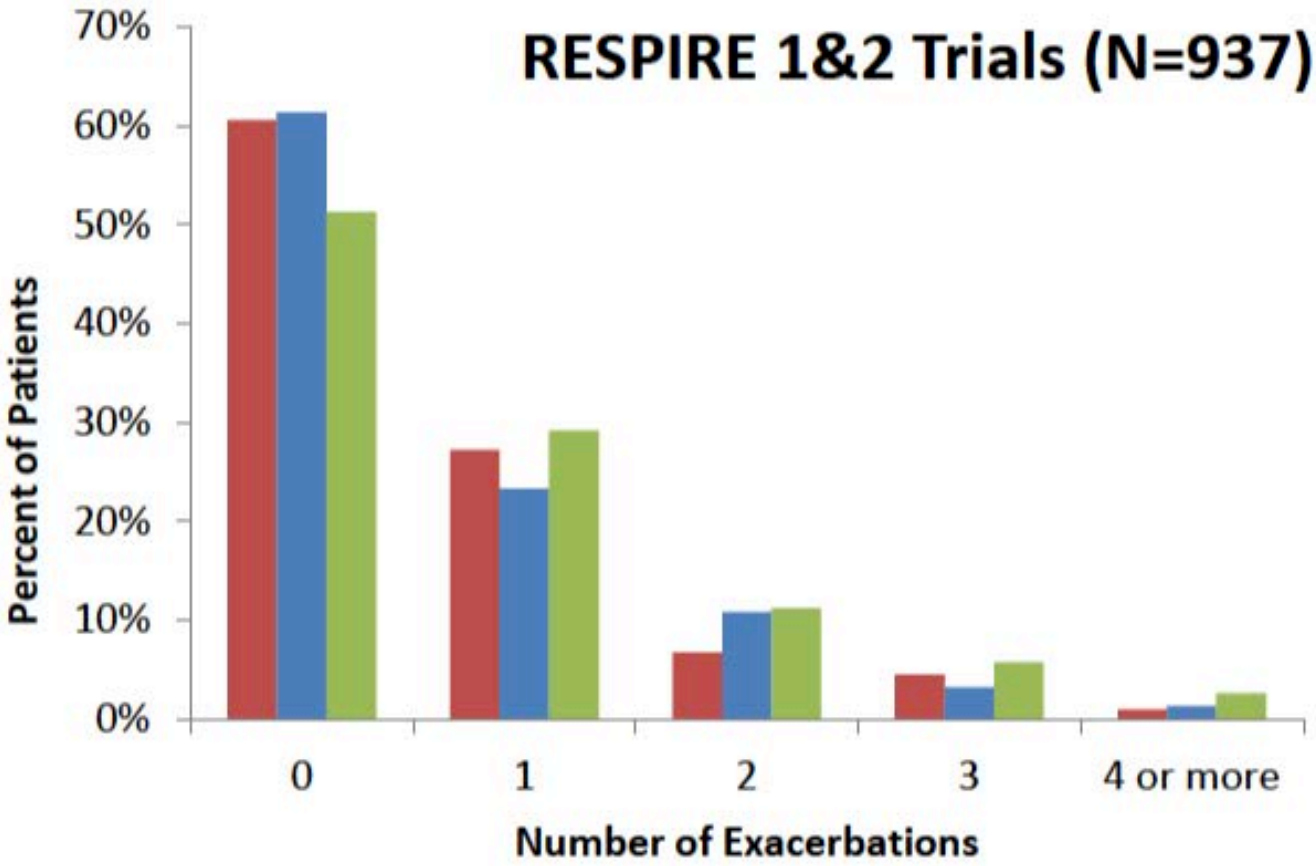
	Percent with PE Cipro vs. Pooled Placebo	**Difference in PE Rate** (Cipro – Placebo)	**Median Time to First PE** Cipro vs. Pooled Placebo	**Days Prolonged with Treatment**	**Hazard Ratio (CI)[2]** (Cipro / Placebo)	**p-value [1]**
CIPRO 28						
RESPIRE 1	67/141 (47.5%) vs. 79/138 (57.2%)	-9.7%	336 vs. 186 days	150 days	0.73 (0.50, 1.07)	p=0.065
RESPIRE 2	56/171 (32.7%) vs. 73/174 (42.0%,	-9.2%	> 336 vs. > 336 days	NE	0.71 (0.39, 1.27)	p=0.051
Combined trials	123/312 (39.4%) vs. 152/312 (48.7%)	-9.3%	> 336 vs. 284 days	> 52 days	0.72 (0.55,0.95)	p=0.008
CIPRO 14						
RESPIRE 1	53/137 (38.7%) vs. 79/138 (57.2%)	-18.6%	> 336 days vs. 186 days	> 150 days	0.53 (0.36, 0.80)	p=0.0005
RESPIRE 2	68/176 (38.6%) vs. 73/174 (42.0%)	-3.3%	> 336 vs. > 336 days	NE	0.87 (0.62, 1.21)	p=0.397
Combined trials	121/313 (38.7%) vs. 152/312 (48.7%)	-9.9%	> 336 vs. 284 days	> 52 days	0.69 (0.52, 0.90)	p=0.002

RESPIRE 1

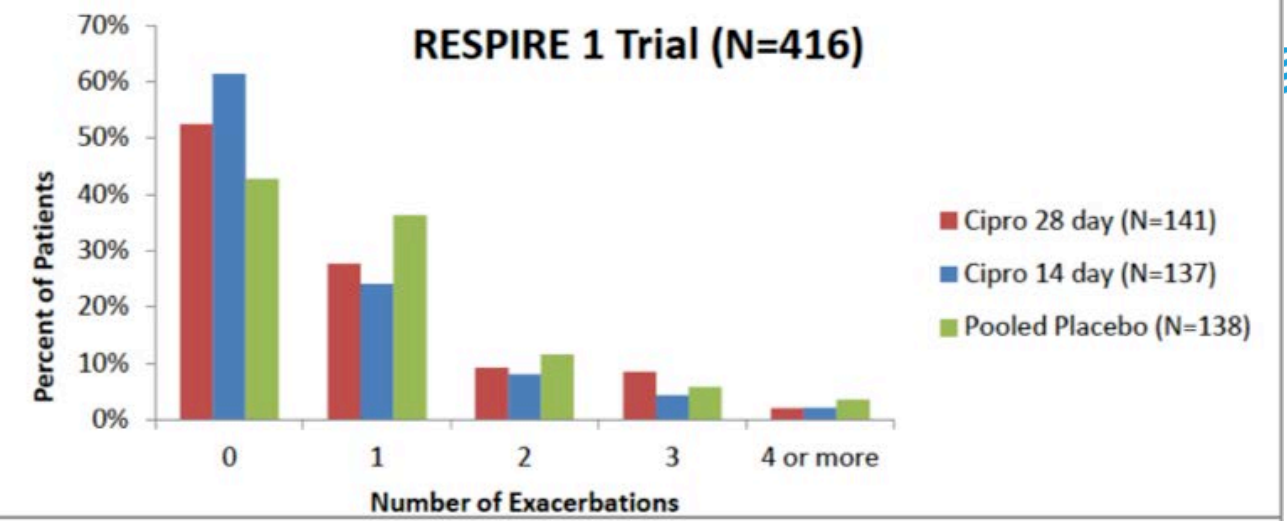
	Ciprofloxacin DPI 14 days on/off	Placebo 14 days on/off	Ciprofloxacin DPI 28 days on/off	Placebo 28 days on/off	Pooled placebo	Total
Patients n	137	68	141	70	138	416
Female	88 (64.2)	44 (64.7)	101 (71.6)	52 (74.3)	96 (69.6)	285 (68.5)
Age years	65.2±13.5	65.5±12.9	64.2±12.1	64.0±13.5	64.8±13.2	64.7±12.9
Idiopathic aetiology	81 (59.1)	43 (63.2)	70 (49.6)	32 (45.7)	75 (54.3)	226 (54.3)
Region[#]						
Europe 1	36 (26.3)	18 (26.5)	35 (24.8)	18 (25.7)	36 (26.1)	107 (25.7)
Europe 2	41 (29.9)	20 (29.4)	42 (29.8)	20 (28.6)	40 (29.0)	123 (29.6)
USA	14 (10.2)	9 (13.2)	14 (9.9)	7 (10.0)	16 (11.6)	44 (10.6)
Latin America	1 (0.7)	0 (0)	3 (2.1)	2 (2.9)	2 (1.4)	6 (1.4)
Japan	11 (8.0)	4 (5.9)	12 (8.5)	6 (8.6)	10 (7.2)	33 (7.9)
Australia/New Zealand	34 (24.8)	17 (25.0)	35 (24.8)	17 (24.3)	34 (24.6)	103 (24.8)

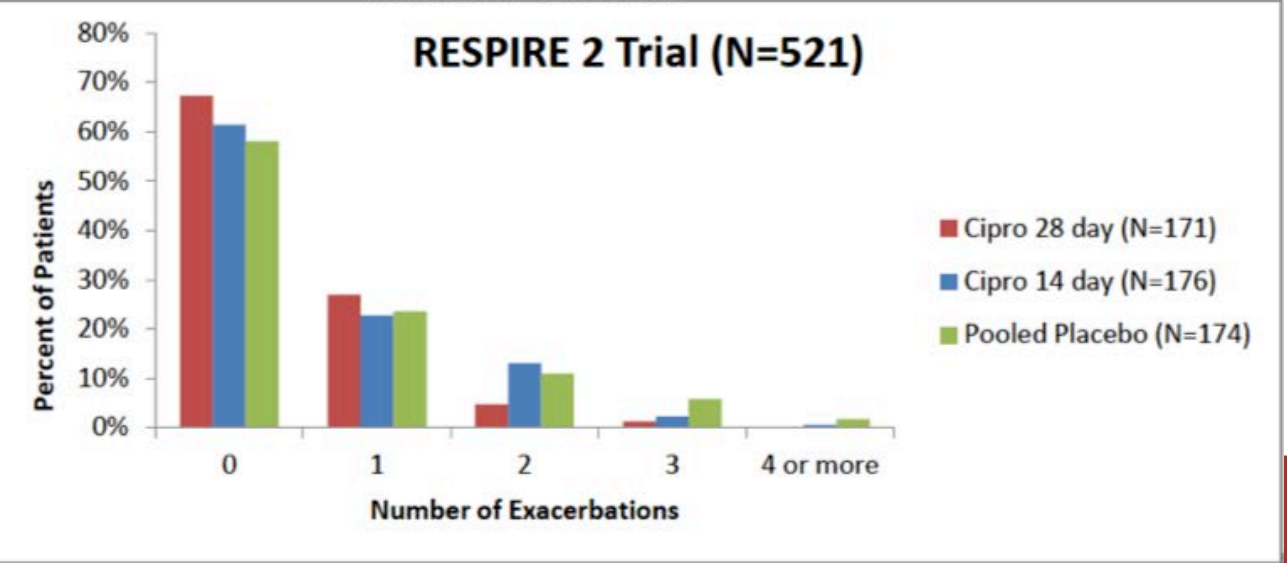
RESPIRE 2

	Ciprofloxacin DPI 14 days on/off	Placebo 14 days on/off	Ciprofloxacin DPI 28 days on/off	Placebo 28 days on/off	Pooled placebo	Total
Patients n	176	88	171	86	174	521
Female	96 (54.5)	62 (70.5)	92 (53.8)	52 (60.5)	114 (65.5)	302 (58.0)
Age years	60.4±13.7	60.4±15.0	59.3±14.2	60.6±13.7	60.5±14.3	60.1±14.0
Idiopathic aetiology	62 (35.2)	32 (36.4)	43 (25.1)	36 (41.9)	68 (39.1)	173 (33.2)
Region[#]						
Europe 1	64 (36.4)	32 (36.4)	65 (38.0)	32 (37.2)	64 (36.8)	193 (37.0)
Europe 2	54 (30.7)	27 (30.7)	54 (31.6)	28 (32.6)	55 (31.6)	163 (31.3)
Africa	0	0	2 (1.2)	0	2 (1.1)	2 (0.4)
Latin America	6 (3.4)	3 (3.4)	7 (4.1)	2 (2.3)	5 (2.9)	18 (3.5)
Asia	39 (22.2)	19 (21.6)	33 (19.3)	17 (19.8)	36 (20.7)	108 (20.7)
Australia	8 (4.5)	4 (4.5)	5 (2.9)	4 (4.7)	8 (4.6)	21 (4.0)
USA	5 (2.8)	3 (3.4)	5 (2.9)	3 (3.5)	6 (3.4)	16 (3.1)



https://www.fda.gov/





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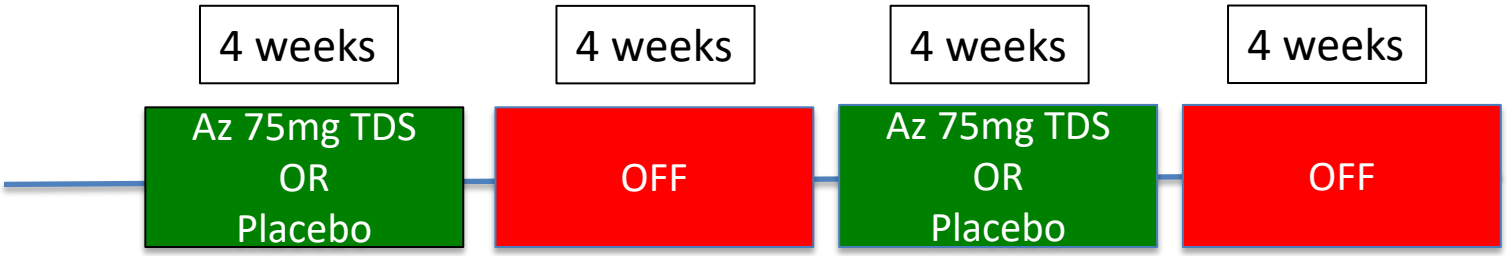
AIR-BX1 and AIR-BX2



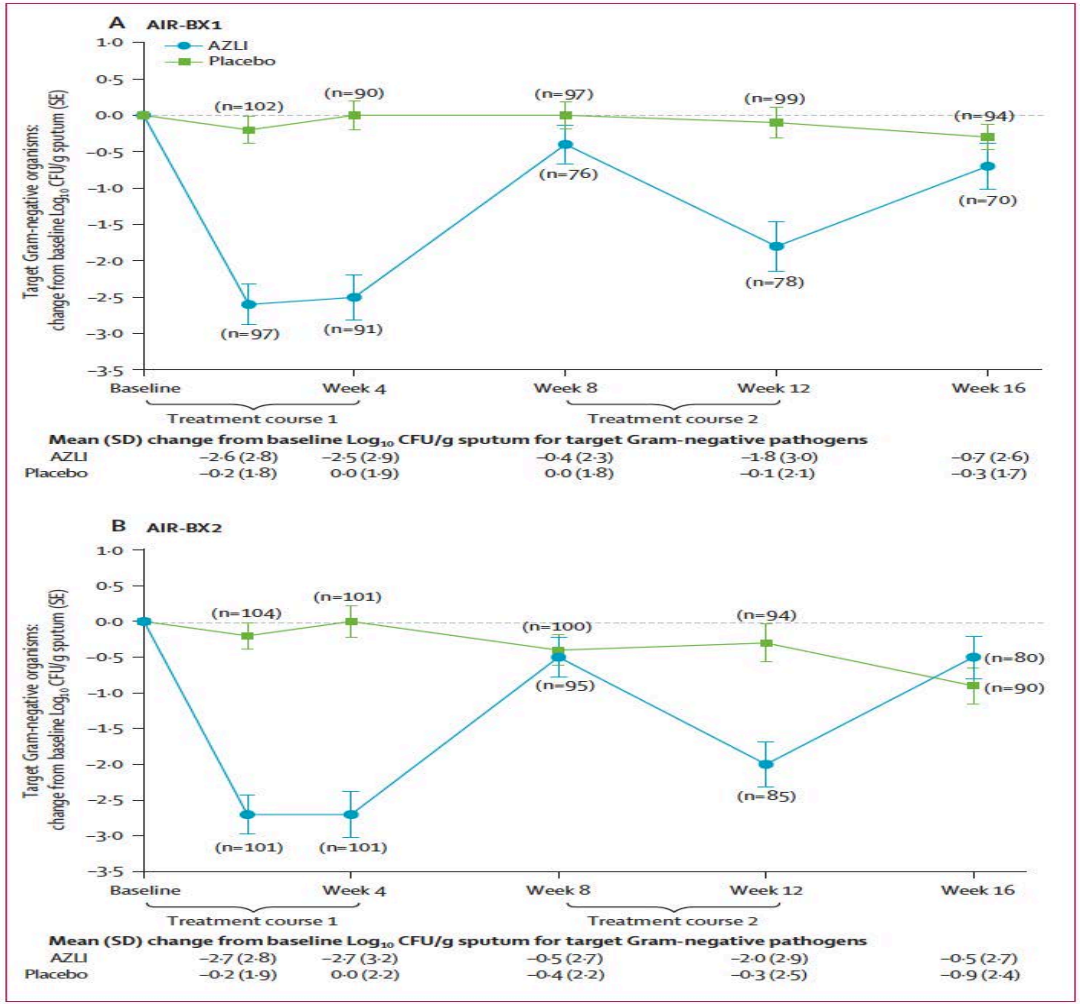


Figure 4: **Mean change from baseline Log_{10} CFU per g of sputum for target Gram-negative organisms**
CFU per g of sputum was imputed as 0 for patients for whom no pathogens were cultured. N=number of patients with available data for change calculations. AZLI=aztreonam for inhalation solution. CFU=colony forming units.

Barker et al Lancet Respir Med 2014

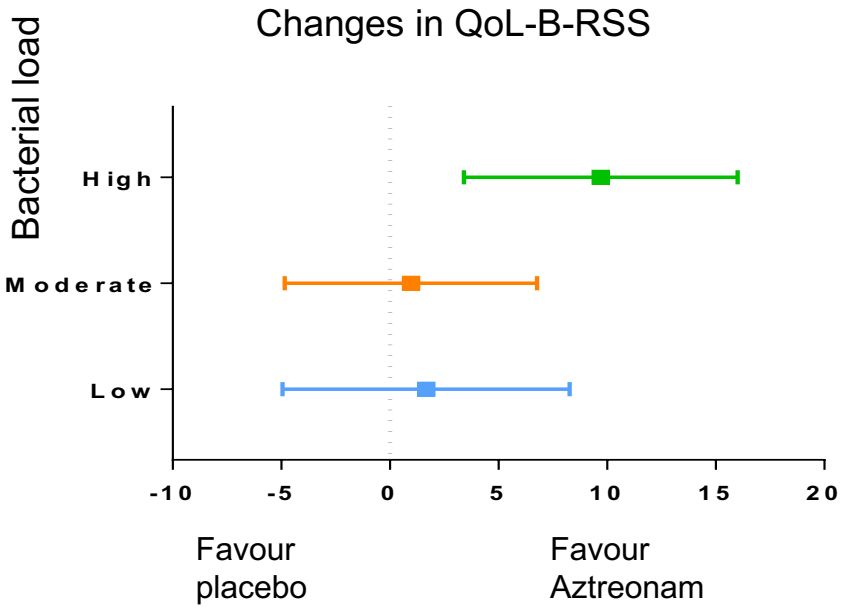
	AIR-BX1				AIR-BX2			
	AZLI (n=134)	Placebo (n=132)	AZLI-placebo difference, HR (95% CI)	p value	AZLI (n=136)	Placebo (n=138)	AZLI-placebo difference, HR (95% CI)	p value
Change from baseline QOL-B-RSS								
At week 4, adjusted mean (SE)	6·4 (1·4)	5·6 (1·4)	0·8 (–3·1 to 4·7)	0·68*	7·9 (1·3)	3·3 (1·3)	4·6 (1·1 to 8·2)	0·011*
At week 12, adjusted mean (SE)	5·7 (1·6)	4·4 (1·5)	1·3 (–3·0 to 5·6)	0·56*	5·2 (1·4)	4·1 (1·4)	1·1 (–2·7 to 5·0)	0·56*
Time to first protocol-defined exacerbation								
Kaplan-Meier estimates of patients with protocol-defined exacerbation at week 16	0·33	0·26	HR 1·26 (0·79 to 1·99)	0·33†	0·33	0·27	HR 1·23 (0·80 to 1·91)	0·35†
Estimated median days (95% CI)	NE	120 (117 to NE)	..	..	NE	NE	..	..

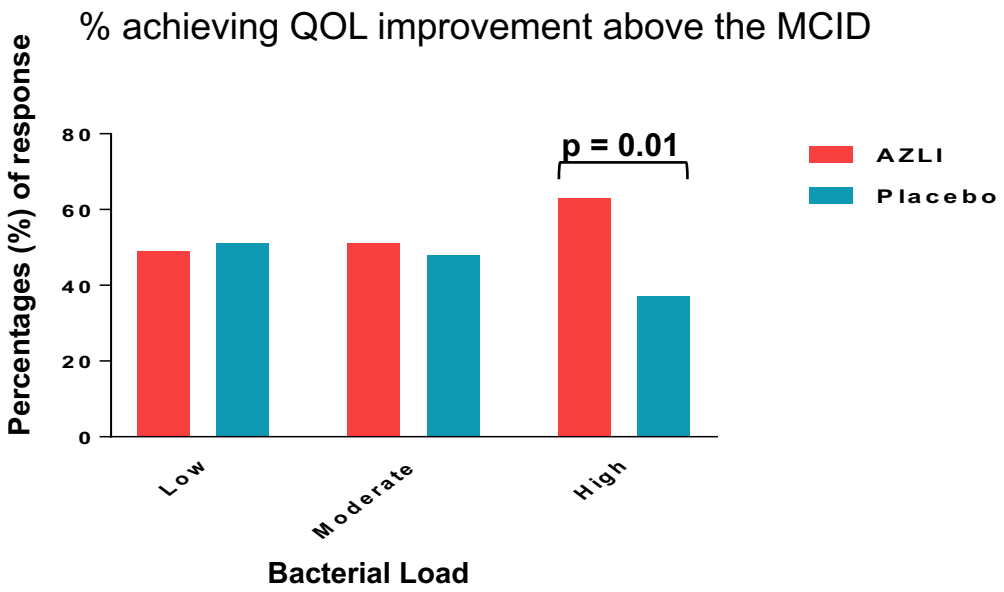
Data are least squares mean (SE) unless otherwise stated. AZLI=aztreonam for inhalation solution. HR=hazard ratio. NE=not estimable. QOL-B-RSS=Quality of Life-Bronchiectasis Respiratory Symptoms scores. *p value is based on *t*-test from mixed effect model repeat measurement model, which included baseline QOL-B-RSS, treatment, visit, and treatment and visit interaction. †p value is based on log-rank test.

Table 2: **Efficacy data**

Barker et al Lancet Respir Med 2014

Re-analysis of the pooled AIR-BX studies stratified for airway bacterial load at baseline





High = >10^7 cfu/g

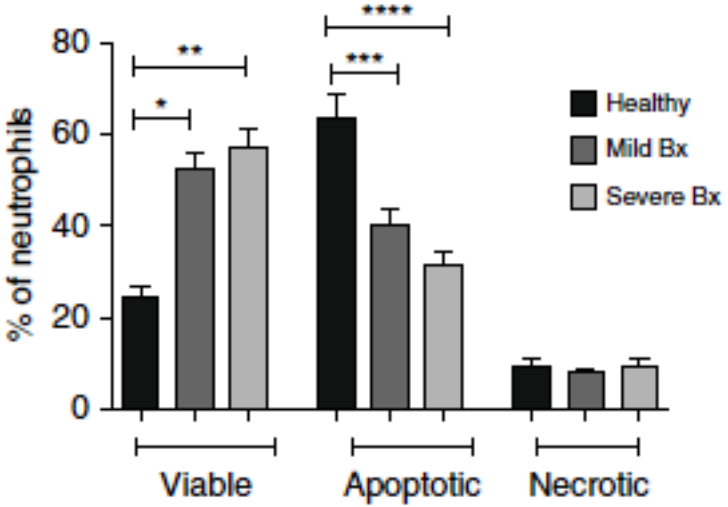
Sibila et al, AJRCCM 2019

What have we learned?

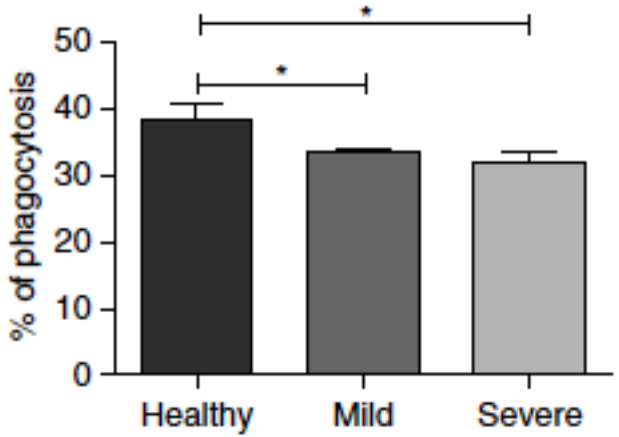
- If you enrole patients who have few exacerbations or low bacterial counts, you won't have a positive trial
- No registered inhaled antibiotic for bronchiectasis at present
- Trials ongoing – tobramycin and colistin in current phase III

Anything else new?

Subtle Immune dysfunction



Bedi et al AJRCCM 2018



Neutrophils from patients with idiopathic bronchiectasis are reprogrammed for longer survival with resulting impaired function.
Same not seen in patients with other active infections (e.g. pneumonia)

Drugs in preclinical and phase I

- Biofilm inhibitors
- Quorum sensing inhibitors
- Antimicrobial peptides
- Iron sequestering agents
- Efflux pump inhibitors
- Nanoparticles of heavy metals (Ag, Au, Zn etc)

Conclusion

- Frustration at failed phase III studies due to poor design
- On going hope for inhaled antibiotics
- Immunomodulators/biofilm inhibitors – watch this space!

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