# Heterogeneous Nature of non-CF Bronchiectasis Aetiology

**Table 1**

Common causes of non-CF bronchiectasis and potential supporting diagnostic features

| Aetiology | Incidence |
|---|---|
| Post-infectious, e.g. pneumonia, pertussis, measles, mycobacterial infections and tuberculosis | 29–42% |
| Allergic bronchopulmonary aspergillosis | 1–8% |
| Immunodeficiency | 1–8% |
| Connective tissue diseases, e.g. rheumatoid arthritis, systemic lupus erythematosis, ankylosing spondylitis, Sjogren's syndrome and relapsing polychondritis | 3–6% |
| Bowel disorders, e.g. inflammatory bowel disease and coeliac disease | 1–5% |
| Aspiration/gastro-oesophageal reflux disease | 1–4% |
| Chronic respiratory disease, e.g. asthma, COPD and alpha-1 antitrypsin deficiency | 1–23% |
| Congenital disorders, e.g. primary ciliary dyskinesia | 1–10% |
| CF | 1–4% |
| Miscellaneous, e.g. endometriosis, amyloidosis, yellow nail syndrome and Young's syndrome | <1% |
| Idiopathic | 26–74% |

M.J. McDonnell, C. Ward, J.L. Lordan, R.M. Rutherford; Non-cystic fibrosis bronchiectasis, *QJM: An International Journal of Medicine*, Volume 106, Issue 8, 1 August 2013, Pages 709–715,

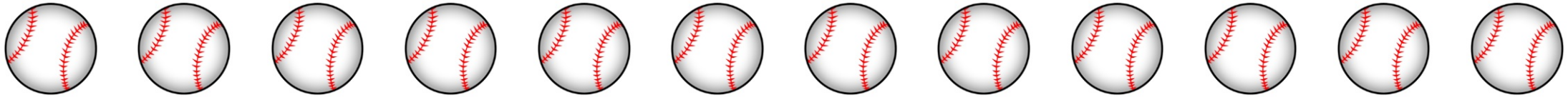
# Heterogeneous Nature of non-CF Bronchiectasis Trial Endpoint

- **CF Bronchiectasis Trial – Will a baseball bat consistently hit a baseball past the infield.**

- **Non-CF Bronchiectasis Trial – Will a baseball bat consistently hit every other style of ball past the infield.**

# Heterogeneous Nature of non-CF Bronchiectasis Participants

- CF Bronchiectasis Trial Participants



- Non-CF Bronchiectasis Trial Participants

# The clinical features of Bronchiectasis associated with Alpha-1 Antitrypsin Deficiency, Common Variable Immunodeficiency, and Primary Ciliary Dyskinesia

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## Background

- Bronchiectasis is associated with rare conditions including Alpha-1 antitrypsin deficiency (AATD), Common Variable Immunodeficiency (CVI) and Primary Ciliary Dyskinesia (PCD). These three rare but important conditions have different pathogenesis and important management considerations.

## Objectives

- The objectives of this study are to compare and contrast the clinical characteristics of bronchiectasis associated with these rare conditions: AATD, CVI and PCD.

## Materials and Methods

**Study inclusion criteria:**

- Adult patients (18 years or older) within the Bronchiectasis Research Registry (BRR)
- Physician established diagnosis of non-cystic fibrosis bronchiectasis
- Presence of AATD, CVI, PCD, or tests negative for the above conditions ("Idiopathic")

**Flow Diagram of the study participants**

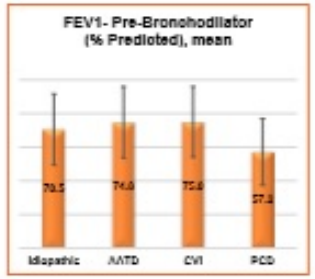

## Results

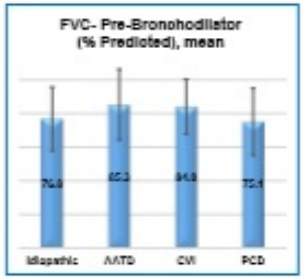
- A diagnosis of bronchiectasis was made at a much younger age in those with PCD than in the other groups ($p<.0001$). Significantly greater proportion of patients with PCD reported pulmonary exacerbations and hospitalizations in the past 2 years compared to AATD, CVI, and idiopathic groups ($p=0.002$ and $p<.0001$, respectively).

**Select baseline demographic and clinical characteristics of the patients in the study sample, n=615**

| | Idiopathic (N=460) | AATD (N=58) | CVI (N=18) | PCD (N=79) | p-value |
|---|---|---|---|---|---|
| Age at enrollment, mean (SD) | 64.2 (15.9) | 66.9 (10.7) | 66.7 (10.5) | 41.9 (14.5) | <.0001 |
| Age at bronchiectasis diagnosis, mean (SD) | 56.5 (15.9) | 60.2 (14.8) | 64.0 (12.5) | 22.8 (15.7) | <.0001 |
| Pulmonary exacerbations in the past 2 years, n (%) | 312 (68.1) | 34 (61.8) | 11 (61.1) | 59 (89.4) | 0.002 |
| Hospitalizations in the past 2 years, n (%) | 83 (18.2) | 11 (19.3) | 8 (44.4) | 28 (48.3) | <.0001 |
| Daily bouts of coughing, n (%) | 373 (81.3) | 42 (72.4) | 11 (64.7) | 71 (91.0) | 0.012 |
| Hemoptysis, n (%) | 100 (21.9) | 11 (18.9) | 3 (16.7) | 19 (25.3) | 0.778 |

- The group with PCD showed a significantly lower mean pre-bronchodilator FEV1 and FVC (% predicted) ($p<0.01$), as well FEV1/FVC ratio than the other groups.

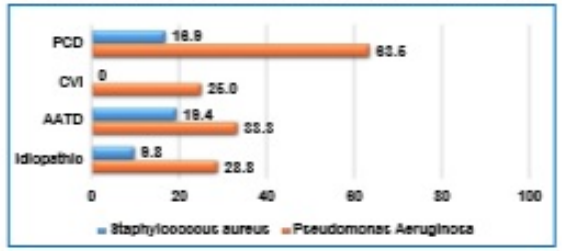



## Results (continued)

- Overall, *Pseudomonas aeruginosa* and *Staphylococcus aureus* were the most commonly reported bacterial isolates from sputum.
- The percentage of patients with PCD reported to be growing *Pseudomonas* in one or more sputum cultures (63.5%) was significantly greater compared to other groups (AATD: 33.3%, CVI: 25.0%, and idiopathic: 28.8%) ($p<.0001$).

**The most prevalent bacterial isolates from sputum at baseline (%)**




## Conclusions

- Our study found that patients with PCD within the BRR are significantly younger, more often report having respiratory symptoms, exacerbations and hospitalizations compared to other groups; their bacterial cultures more frequently show presence of *Pseudomonas aeruginosa*.

## Acknowledgements

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## References

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Parr DG, Guest PG, Reynolds JH, et al. Prevalence and impact of bronchiectasis in alpha1-antitrypsin deficiency. Am J Respir Crit Care Med 2007;

Barker AF. Bronchiectasis. New England Journal of Medicine 2002;

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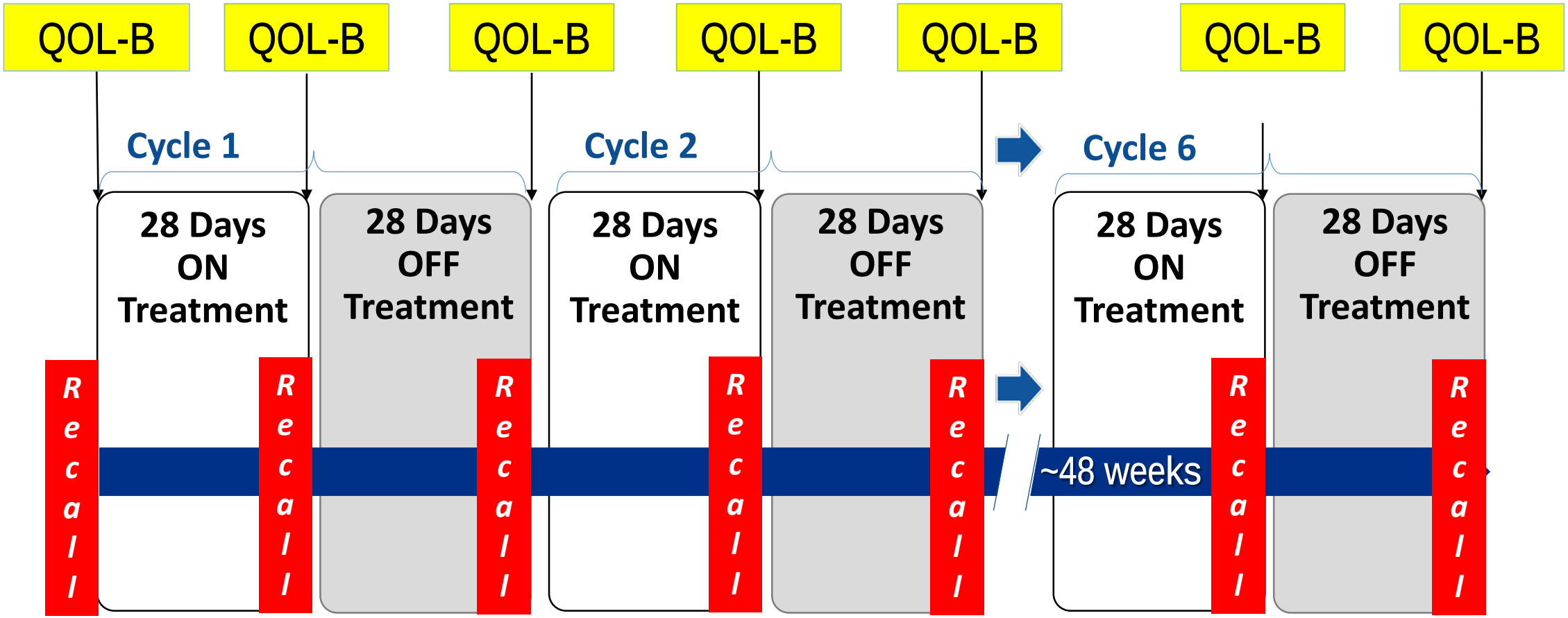
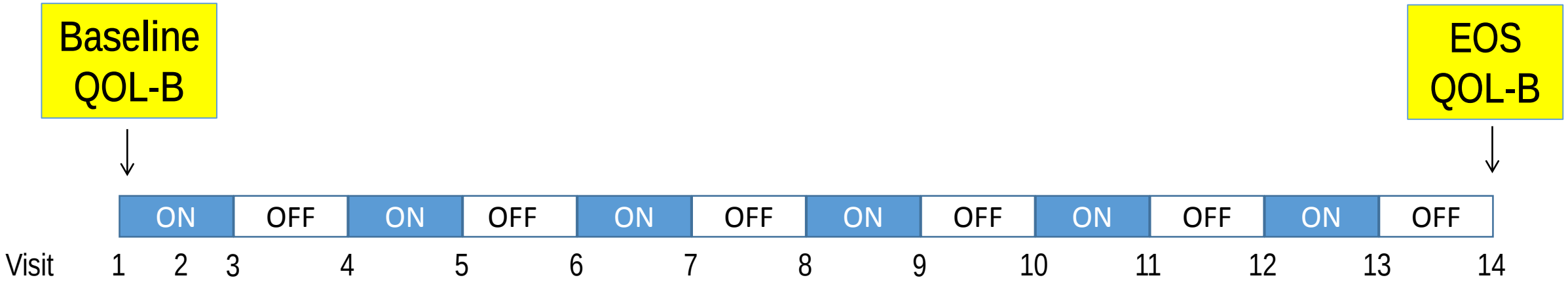
# Quality of Life Using the QOL-B Instrument Measured every 28 Days, with 7 Day Recall




From Aradigm FDA hearing January 11, 2018.

# Prespecified Quality of Life Endpoint

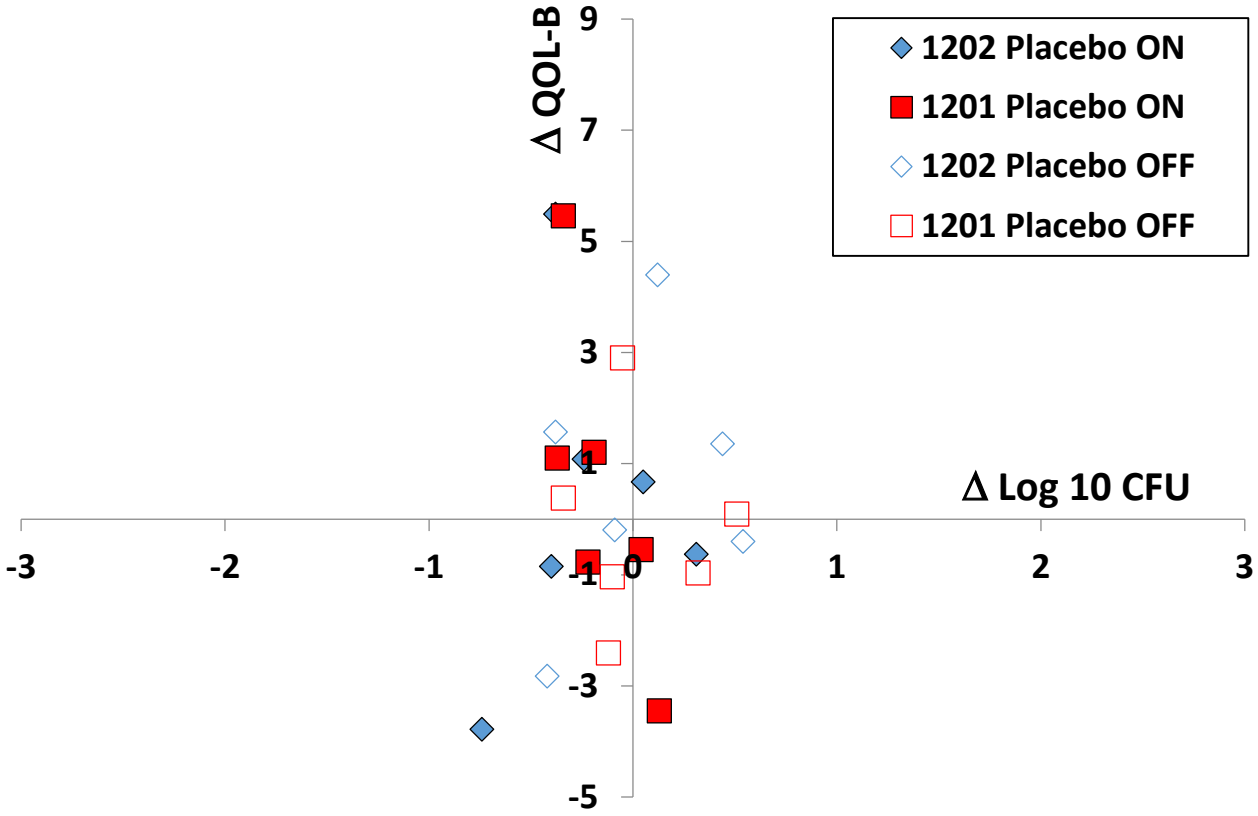
- Secondary Endpoint
  - QOL-B comparing baseline (before medication taken) to Week 48 (28 days after the last treatment)




From Aradigm FDA hearing January 11, 2018.

# Placebo: Visit to Visit Changes in QOL-B Appear to Be Random as Are Small Changes in Colony Forming Units of *Pseudomonas aeruginosa*

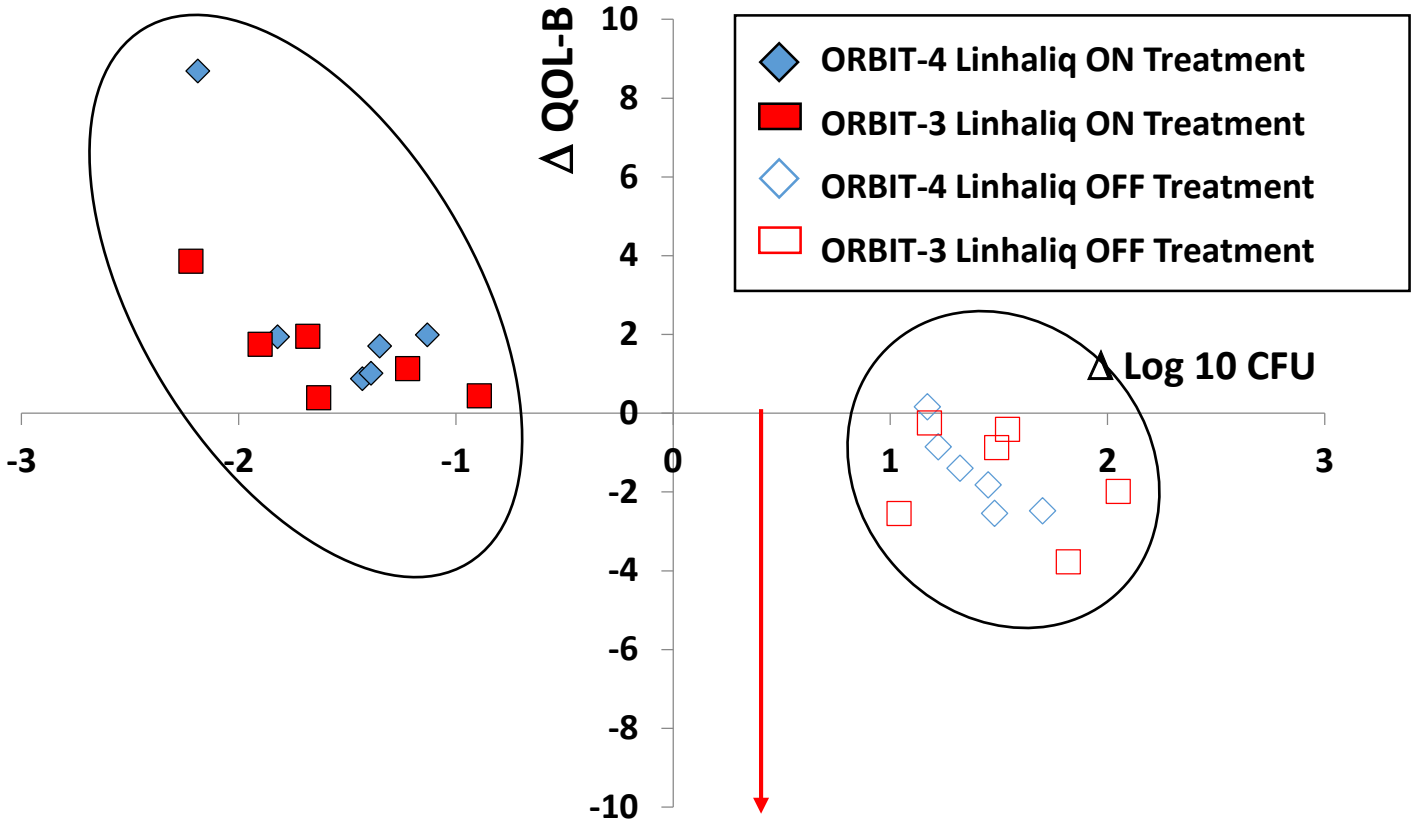
- Minimal changes in CFUs during ON and OFF periods
- OFF Periods just as likely as ON Periods to have positive changes in QOL-B




Each data point represents the mean delta QOL-B for all patients during that treatment cycle  There are 6 on-treatment periods and 6-off treatment periods per study

From Aradigm FDA hearing January 11, 2018.

# Linhaliq: Visit to Visit Changes in QOL-B are Correlated with Visit to Visit Changes in CFUs of *Pseudomonas aeruginosa*




**Large reduction in QOL-B observed around the time of a pulmonary exacerbation**

Each data point represents the mean delta QOL-B for all patients during that treatment cycle There are 6 on-treatment periods and 6-off treatment periods per study

From Aradigm FDA hearing January 11, 2018.

# QOL Summary from Aradigm Trial

- The prespecified endpoint compared QOL-B at two time points when the patients were not on the trial medication
- Compared to each previous visit, patients treated with Linhaliq reported
  - Improvement in QOL-B at the end of each on-treatment period and worsening of the QOL-B at the end of each off-treatment period, consistent with the changes of the load of *P. aeruginosa* in their sputum
- Compared to each previous visit, patients treated with Placebo reported
  - Changes in QOL-B that appeared random
- Occurrence of a pulmonary exacerbation was associated with a big drop in QOL-B, consistent with the report from the bronchiectasis trial with Cayston (Quittner et al., 2015)

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