Methods: 89 patients from 14 sites were randomized to either azithromycin 250 mg daily or placebo, for 12 months. All were reviewed at three-monthly intervals during treatment and at 3 month's follow-up. At each review the following were assessed; exacerbation frequency (being the primary endpoint), lung function, qualitative and quantitative sputum bacteriology, serum and sputum inflammatory markers, adverse effects, symptom scores and St George's respiratory questionnaire. High resolution CT-scans were performed at study entrance and end of study.
Primary results: 81 patients completed the study. At the end of 12 month's treatment the azithromycin group showed a significant reduction in exacerbation frequency as compared to the placebo treated group (1,28/year, SD 1,32 vs 2,67/year, SD 1,95, $p<0.0001$). No significant differences were found with respect to lungfunction, inflammatory markers and adverse effects between groups.
Conclusions: Longterm azithromycin treatment significantly reduces exacerbation frequency in patients with non-CF bronchiectasis, without additional side effects.

241. Advances in antibiotic therapy of non-cystic fibrosis bronchiectasis

1924
Long term azithromycin treatment: A randomised placebo-controlled trial in non-CF bronchiectasis; results from the BAT trial
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Introduction: Bronchiectasis arises from an ongoing cycle of inflammation and bacterial colonization and has a major impact on a patient's wellbeing, mainly because of frequent infectious exacerbations.
Aim: Assessing the efficacy of longterm azithromycin treament over 1 year in patients with non-cystic fibrosis bronchiectasis in a randomized placebo controlled trial.

1925
Multicenter, randomized, double-blind, placebo-controlled study (ORBIT 1) to evaluate the efficacy, safety, and tolerability of once daily ciprofloxacin for inhalation in the management of *pseudomonas aeruginosa* infections in patients with non-cystic fibrosis bronchiectasis
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CFI (Ciprofloxacin for Inhalation) is being developed as a chronic intermittent therapeutic agent to manage cystic fibrosis (CF) and non-CF bronchiectasis (BE) patients colonized with *Pseudomonas aeruginosa (PA)*. CFI is a once a day inhaled liposomal controlled release formulation to achieve adequate sustained concentration of ciprofloxacin in the lung while minimizing potential for local and systemic side effects. Following a successful study in non-CF BE with 2 doses (6 mL (300 mg ciprofloxacin) or 3 mL (150 mg ciprofloxacin) we completed a randomized, multicentre, double-blind, placebo-controlled trial (ORBIT 1), evaluating even lower inhaled doses of CFI (3mL (150 mg ciprofloxacin) or 2 mL (100 mg ciprofloxacin) in 96 patients non-CF BE subjects. Aside from evaluating the mean decreases against placebo in the *PA* colony forming units, changes in QoL, lung function and 6 min walk will be assessed. In the open label study in 36 patients with non-CF BE CFI was well tolerated and both doses demonstrated significant mean decreases against baseline in the *PA* colony forming units (CFUs) at 28-days of 3.5 $\log_{10}$ ($p<0.001$) and 4.0 $\log_{10}$ ($p<0.001$) units, respectively, in the per protocol (PP) population. High concentration of ciprofloxacin was found in the sputum. No bronchodilator treatment was needed before or during inhaled study dug treatment. Primary efficacy data from ORBIT 1 will be presented at the ERS. Supported by Aradigm Corporation.

1926
Airways reflux contributes to cough severity and airways inflammation in non-CF bronchiectasis
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Objective: To assess the impact of airways reflux on clinical severity and airway inflammation in bronchiectasis.
Method: Patients with bronchiectasis completed the Hull airways reflux questionnaire (HARQ,which has been validated for use in assessing airways refux as a cause of cough). The minimum score was 0 and maximum 70. A score of >13 was indicative of reflux. Patients were followed-up with longditudinal spirometry, sputum culture and Leicester cough questionnaire (LCQ) as a measure of cough

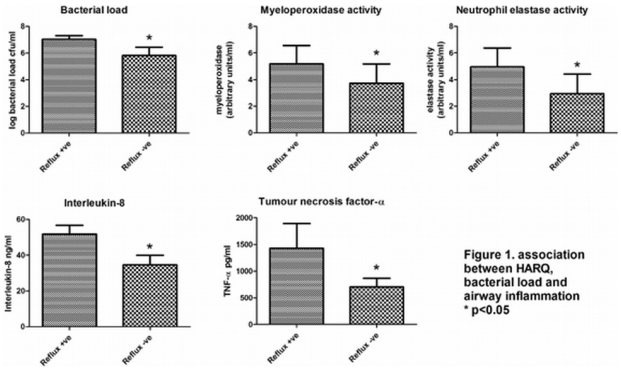

Figure 1. association between HARQ, bacterial load and airway inflammation
* p<0.05

severity (3-severe and 21-no cough). Myeloperoxidase (MPO), neutrophil elastase (NE), interleukin-8 (IL-8) and tumour necrosis factor-alpha (TNF-α) were measured from spontaneous sputum samples. Multivariable linear regression was used to determine independent factors associated with cough severity (LCQ).
Result: 187 completed the study. 58.2% were female. Median age was 65 years. 77.5% had reflux using HCQ.
Reflux+ve patients had more severe cough symptoms as per LCQ (15.2 (3.5) vs.19.4 (1.9)), $p<0.001$. Sputum levels of MPO, NE, IL-8, TNF-α and IL-1β were significantly higher in reflux+ve group ($p<0.0001$ for all comparisons).
After adjusting for age, gender, co-morbidities, disease severity and chronic colonisation, reflux was independently associated with cough severity (-3.27 standard error 0.81, p=0.0002).
Conclusion: The presence of airways reflux is associated with more severe cough and increased airway inflammation in bronchiectasis.

1927

The relationship between airway bacterial load and airways inflammation in stable non-cystic fibrosis bronchiectasis

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Objective: To investigate the relationship between airway bacterial load and markers of airways inflammation in stable patients with bronchiectasis.
Methods: 302 patients with non-CF bronchiectasis confirmed by HRCT were enrolled. At 6 monthly review, spontaneous sputum samples were processed to determine bacterial load, expressed as $\log_{10}$ colony forming units/ml (cfu/ml). Sputum sol was analysed for myeloperoxidase (MPO) and neutrophil elastase elastase activity. Interleukin-8 (IL-8), Interleukin 1-beta (IL-1β) and tumour necrosis factor alpha (TNF-α) were measured by ELISA.
Results: 67 patients (22.1%) of patients grew no pathogens. Pathogenic microorganisms were obtained in 77.9% of patients, most frequently *Haemophilus influenzae* (37.4% of isolates), *Pseudomonas aeruginosa* (20.4%), *Staphylococcus aureus* (13.2%), *Streptococcus pneumoniae* (11.9%) and *Moraxella catarrhalis* (10.6%).
Airway inflammation increased progressively with increasing bacterial load. Statistically significant differences were observed, when compared to patients with no pathogens, at bacterial loads above 1×10^6cfu/ml for MPO (p=0.01), neutrophil elastase activity (p=0.006) and IL-8 (p=0.02), and above 1×10^7 for TNF-α (p=0.04) and above 1×10^5 for IL-1β (p=0.003).

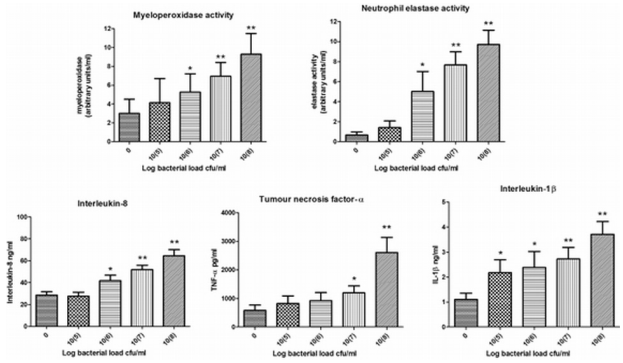

Figure 1. *p<0.05, **p<0.0001.

Conclusion: There is a direct relationship between airway bacterial load and the degree of airway inflammation in stable bronchiectasis.

1928

Dual release ciprofloxacin for inhalation (DRCFI) reduces sputum *pseudomonas aeruginosa* (*Pa*) density and delays time to infective pulmonary exacerbation in non-cystic fibrosis (CF) bronchiectasis (BE)

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Prior studies of inhaled therapies with proven efficacy in CF have failed to translate into beneficial treatments for non-CF BE and even suggested potential for harm. Novel, effective therapies for non-CF BE are urgently needed. DRCFI is a novel liposomal formulation which delivers the antibiotic in a controlled way resulting in an initial high peak of ciprofloxacin followed by prolonged high concentrations of the antibiotic in the lung. In this 24 week Phase 2 multicentre, double-blind trial, 42 BE subjects with chronic *Pa* infection were randomized to once daily inhaled DRCFI or matching inhaled placebo for three treatment cycles (28 days on, 28 days off). DRCFI resulted in a highly significant reduction in the primary outcome measure in sputum *Pa* density at 28 days of 4.2 $\log_{10}$ units in the DRCFI group, vs a decrease of 0.1 $\log_{10}$ units in the placebo group. 17 subjects in the placebo group required supplemental antibiotics for respiratory-related infections versus 8 subjects in the DRCFI group (p=0.05). DRCFI demostrated a delay in the median time to first exacerbation of 58 days in the placebo group versus 134 days in the DRCFI group. In contrast to prior studies of nebulized antibiotics in this patient group, DRCFI was well tolerated overall. Fewer respiratory adverse events occurred in the DRCFI group compared to the placebo group and overall the incidence and severity of all other adverse events were similar. In subjects with non-CF BE, DRCFI is well tolerated, has a potent anti-Pseudomonal effect and significantly delays time to exacerbation.
Supported by Aradigm Corporation.

1929

Efficacy and safety of ciprofloxacin dry powder for inhalation in patients with non-cystic fibrosis bronchiectasis

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Introduction: Ciprofloxacin dry powder for inhalation (DPI) uses PulmoSphere™ technology to target the lungs of patients chronically colonized with bacterial pathogens.
Objective: This phase II study assessed the efficacy and safety of ciprofloxacin DPI treatment for 28 days in non-cystic fibrosis bronchiectasis (non-CF BE) patients.
Methods: Adult patients with pulmonary stable non-CF BE received twice-daily 32.5 mg ciprofloxacin (50 mg ciprofloxacin DPI) or matching placebo for 28 days, with a 56-day follow-up. The primary endpoint was reduction in total bacterial load in sputum at end of treatment (EOT) compared with placebo.
Results: The mean baseline characteristics in the intent-to-treat population (N=124) were: age 63, weight 70 kg, FEV1 56% of predicted. At EOT, ciprofloxacin DPI reduced mean bacterial load by 3.6 logs, vs 0.3 logs with placebo ($p<0.001$), and median CRP level was 2.45 mg/l lower compared with placebo (not significant). Mean difference in the St George's Respiratory Questionnaire at EOT was 3.6 points between treatment arms ($p=0.059$). Fewer patients treated with ciprofloxacin DPI than with placebo experienced an exacerbation requiring antibiotic treatment (23% vs 28%, not significant). The adverse event rate was similar in both treatment arms. Very few bronchospasms occurred (n=6, 2 after EOT). They were equally distributed between both groups.
Conclusions: Ciprofloxacin DPI significantly reduced bacterial load in patients with non-CF BE ($p<0.001$) and was well tolerated. Several secondary endpoints showed a trend in favour of ciprofloxacin DPI. Ciprofloxacin DPI is a promising candidate for investigating benefits of long-term therapy in non-CF BE patients.

1930

Antimicrobial efficacy of ciprofloxacin dry powder for inhalation in patients with non-cystic fibrosis bronchiectasis

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Introduction: Ciprofloxacin dry powder for inhalation (DPI) is a formulation (PulmoSphere™ technology) in development for long-term therapy of non-cystic fibrosis bronchiectasis (non-CF BE). This phase II, randomized, double-blind study was designed to assess efficacy and safety over 28 days in non-CF BE patients with positive sputum culture for predefined respiratory pathogens (RPs).
Methods: Adult patients with non-CF BE received 32.5 mg ciprofloxacin (50 mg ciprofloxacin DPI) or matching placebo bid for 28 days, with a 56-day follow-up. The primary endpoint was reduction in total bacterial load in sputum at end

of treatment (EOT). In addition, eradication of RPs and reduction of individual species was documented.

Results: The primary endpoint of significant reduction in bacterial load of RPs at EOT was achieved ($\log_{10}$ –3.6 vs –0.3 for placebo, $p<0.001$). In addition, greater reductions and eradications were achieved for the major pathogenic species including, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*. The eradication rates for the baseline pathogens at EOT were 35% vs 8% for placebo. At EOT, eradication was achieved in all patients infected at baseline with *M. Catarrhalis* and in all but 1 patient infected with *H. influenzae.*

Conclusions: Ciprofloxacin DPI achieved a significantly greater reduction in total bacterial burden than placebo. A promising trend in reduction and eradication of the major pathogenic species was also noted. Ciprofloxacin DPI has demonstrated promise for long-term inhalation therapy to reduce the major pathogenic species in non-CF BE, which could reduce the incidence of exacerbations.