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Moxifloxacin vs amoxicillin/clavulanic acid in outpatient AECOPD: MAESTRAL results

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Running title: moxifloxacin vs co-amoxiclav in AECOPD

Abstract

Bacterial infections causing acute COPD exacerbations (AECOPD) frequently require antibacterial treatment. More evidence is needed to guide antibiotic choice.

MAESTRAL was a multiregional, randomised, double-blind non-inferiority outpatient study. Patients were ≥60 years, with an Anthonisen type 1 exacerbation, FEV_1<60% predicted and ≥2 exacerbations in the last year. Following stratification by steroid use patients received moxifloxacin 400 mg PO q.d. (5-days) or amoxicillin/clavulanic acid 875/125 mg PO b.d. (7-days). The primary endpoint was clinical failure 8-weeks post-therapy in the per protocol (PP) population.

Moxifloxacin was non-inferior to amoxicillin/clavulanic acid at the primary endpoint (111/538, 20.6% vs 114/518, 22.0%, 95% CI –5.89, 3.83). In patients with confirmed bacterial AECOPDs, moxifloxacin led to significantly lower clinical failure rates than amoxicillin/clavulanic acid (ITT with pathogens, 62/327, 19.0% vs 85/335, 25.4%, *P*=0.016). Confirmed bacterial eradication at EOT was associated with higher clinical cure rates at 8-weeks post-therapy overall (*P*=0.0014) and for moxifloxacin (*P*=0.003). Patients treated with oral corticosteroids had more severe disease and higher failure rates.

The MAESTRAL study showed that moxifloxacin was as effective as amoxicillin/clavulanic acid in the treatment of outpatients with AECOPD. Both therapies were well tolerated.

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD), which is usually associated with chronic bronchitis, cause substantial morbidity, mortality and a marked reduction in quality of life [1–4], placing a significant burden on both patients and healthcare systems [5–7]. Frequent exacerbations result in a more rapid reduction in lung function, with even single episodes having a prolonged negative effect on health status [8,9]. One factor that may result in high relapse rates is persistent bacterial infection [10].

Few trials show clinical or bacteriological superiority of one antibiotic over another in acute exacerbations of chronic bronchitis (AECB) or AECOPD, possibly due to issues of sample size, patient selection and endpoint definition [11]. Many clinical studies have enrolled highly heterogeneous patient populations in terms of age, comorbidities, and importantly, disease severity [12]. Current treatment guidelines recommend antibiotic therapy for more severely ill patients [13–15] and often use acute symptom change based on Anthonisen criteria of type I (worsening dyspnoea with increased sputum volume and purulence) or II (change in any two of these symptoms) exacerbations to define this group. Patients with such exacerbations are the most likely to benefit from antibiotics, suggesting a bacterial aetiology [16]. Inclusion in trials of patients with type III exacerbations (change in any one symptom) and those with mild COPD may distort the true effect of antibiotics as such patients are likely to experience recovery without antimicrobial. Most clinical trials have focussed on short-term clinical efficacy with test of cure being a few days or weeks after the end of treatment. However, as the time course of recovery can be lengthy [17] and as some patients remain at risk of further exacerbations for several weeks after treatment [18,19] monitoring patients over this prolonged period may provide a more accurate picture of the true efficacy of an antibiotic therapy. It is likely that a rapid relapse relates to incomplete resolution of the previous exacerbation rather than a second new exacerbation.

Comparing a large group of patients with moderate-to-severe COPD treated with moxifloxacin or amoxicillin/clavulanic acid – two treatments recommended in this group [14,15] – at a novel 8 week endpoint may help identify patients that could benefit from one or other antibiotic. The choice of an eight week timepoint captures

relapses that are likely related to management of the initial exacerbation, but is not so long that other events, such as antibiotic treatment of a non-respiratory condition, make interpretation of results difficult. The primary objective of the MAESTRAL (Moxifloxacin in AECBs Trial) is to compare the efficacy of a 5-day course of moxifloxacin to that of a 7-day course of amoxicillin/clavulanic acid in the treatment of outpatients with chronic bronchitis experiencing AECOPD who are at high risk of treatment failure. MAESTRAL may provide information that supports current guidelines and recommendations in terms of which treatments are most appropriate for specific patient groups, in particular those with confirmed bacterial infections, as well as further evidence regarding the most appropriate study design for trials of antibiotics in outpatients with AECB/AECOPD.

Methods

Full details of the complete study design have been published previously [20] and are available online.

Study design and treatments

MAESTRAL (NCT00656747) was a prospective, multinational, multicentre, randomised, double-blind, double-dummy controlled, non-inferiority study that compared the efficacy of 5 days of moxifloxacin 400 mg PO once-daily with 7 days of amoxicillin/clavulanic acid 875/125 mg PO twice daily as a first therapy in outpatients experiencing an AECOPD. The dose of amoxicillin/clavulanic acid was selected based on that which is most commonly used, recommendations in treatment guidelines, and data showing the equal efficacy but better tolerability profile of the 875/125 mg b.d. dose vs the 500/125 mg t.d.s dose [21]. Prior to randomisation, patients were stratified based on the concomitant administration of a short course of oral steroids, prescribed at the treating physician's discretion (see Supplementary Material for full details). Compliance was assessed via collection of empty and/or unused packs of the study drug at EOT or the premature discontinuation visit. All patients provided written informed consent and the study was carried out according to relevant ethical and Good Clinical Practice Guidelines.

Patients

Full inclusion and exclusion criteria are given in Supplementary Material. In brief, outpatients with moderate-to-severe COPD [14]) and chronic bronchitis suffering from an Investigator-evaluated Anthonisen type I exacerbation and who were considered by

the Investigator to require antibiotic therapy were enrolled. Patients were at least 60 years old with a documented history of two or more exacerbations within the previous year requiring a course of systemic antibiotics and/or systemic corticosteroids and were current or past cigarette smokers (≥20 pack-year smoking history). At enrolment, all patients had a post-bronchodilator forced expiratory volume in 1 second (FEV_1) ≤60% predicted, with FEV_1/forced vital capacity (FVC) <70%.

Microbiology

Spontaneous sputum samples were obtained from all patients and assessed in a local laboratory by Gram stain and culture. The first sputum sample was collected at the enrolment visit, with 'first-morning samples preferred for subsequent visits. Investigators carried out macroscopic quality assessments of all samples and neutrophil levels were assessed semi-quantitatively. Pre-specified potentially pathogenic bacteria (PPB) (*Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Haemophilus* spp.*, Enterobacteriaceae* spp. and *Staphylococcus aureus*) were identified. Full details of susceptibility testing [22] are given in the Supplementary Material.

Endpoints

The primary efficacy endpoint of MAESTRAL was clinical failure by the 8-weeks post-therapy visit. Clinical failure was defined as the requirement for additional or alternate treatment with systemic antibiotics and/or systemic corticosteroids (including increased dose or duration of treatment), and/or hospitalisation within 8 weeks post-therapy for an exacerbation of respiratory symptoms. Prior to unblinding, an independent Data Review Committee (DRC) assessed the data for all patients who were clinical failures or had indeterminate assessments in order to confirm the primary clinical outcome. Secondary endpoints included clinical response in patients with positive sputum cultures and bacteriological outcomes. A full list is available in Supplementary Material.

Statistical analyses

The statistical analysis plan, including definitions of clinical and bacteriological response, is reported in full in Wilson *et al.*, [20] and is included in the Supplementary Material. The primary aim of the study was to show non-inferiority (defined as a difference in failure rates of ≤6% using a one-sided test at a level of 2.5%) of

moxifloxacin vs amoxicillin/clavulanic acid in the per protocol (PP) population (see Figure 1 for definitions of populations). If non-inferiority was statistically proven, the possibility that moxifloxacin is superior to amoxicillin/clavulanic acid was tested in the intent-to-treat (ITT) population, using a one-sided test at the 2.5% level. The primary ITT analysis was clinical failure vs all other evaluations (clinical cure, indeterminate and missing). Two sensitivity analyses in the ITT population are outlined in the Supplementary Material. Efficacy outcomes in bacteriologically positive patients were assessed in the PP and ITT with pathogens populations. Other secondary clinical endpoints were analysed using appropriate patient populations and time points (see Supplementary Material). There was no alpha level adjustment for the secondary efficacy variables or the subgroup comparisons that were carried out. All safety events were assessed by the investigator based on clinical investigation and patient interview. All patients were also required to record any symptoms indicative of an adverse event, which were then scrutinized by the investigator. All events were assessed by the investigator for relatedness to the study drugs.

Results

Patients

A total of 1492 patients from 30 countries were enrolled in the study, of whom 1372 were randomised, and 1056 were valid (PP) for the primary efficacy analysis (twenty were excluded from the ITT population) (Figure 1). Reasons for exclusion from the PP population (moxifloxacin, n=139; amoxicillin/clavulanic acid n=157) were similar for both treatment groups, the most common being violation of inclusion/exclusion criteria, clinical responses of indeterminate, and patients lost to follow up. Criteria violations leading to exclusion are listed in the Supplementary Material. Patient characteristics at baseline are shown in Table 1 and were similar between treatment groups: the majority of patients were Caucasian men, at least 65 years old with moderate-to-severe airway obstruction. A majority of patients in each group had co-morbid conditions (moxifloxacin 78%, amoxicillin/clavulanic acid 81%) and were receiving maintenance therapy for their COPD (Table 1). Further details of the most frequent co-morbid conditions are listed in the Supplementary Material. No marked differences in patient characteristics were seen between the ITT and PP populations.

A total of 371 PP patients (35.1%) received concomitant steroid therapy (moxifloxacin, n=182; amoxicillin/clavulanic acid, n=189) with steroid use varying by region (Asia/Pacific, 92/322, 28.6%; Europe 130/375, 34.7%; South Africa 17/35, 48.6%; Latin America 131/310, 42.2%; Canada 1/14, 7.1%). Compared with the non-steroid group, these steroid-treated patients patients had a mean lower % predicted FEV at enrolment (overall: 36.8 ±11.4L vs 39.2±11.4 L; *P*<0.0001) and a higher proportion of patients had an FEV_1 <30% (overall: 29.9% vs 22.9%; *P*=0.017). We conducted retrospective analyses (shown in the Supplementary Material) which indicate that steroid-treated patients had: a longer past history of respiratory disease, more cough and wheeze at baseline, were more breathless with tachypnea and tachycardia and had worse scores on AECB-SS health status questionnaires.

Primary efficacy analysis

Moxifloxacin was non-inferior to amoxicillin/clavulanic acid with respect to clinical failure rates at 8 weeks post-therapy in the PP population (20.6% vs 22.0%, respectively, 95% CI –5.89%, 3.83%; Table 2). The analysis of the ITT population also demonstrated non-inferiority, 95% CI –5.50, 3.03, but did not demonstrate superiority (Table 2).

Secondary efficacy analysis

Clinical failure rates in patients with bacteria isolated at baseline were significantly lower in moxifloxacin vs amoxicillin/clavulanic acid-treated patients, with a treatment difference of approximately 6% in favour of moxifloxacin in both the PP with pathogens (50/260, 19.2% vs 68/261, 26.1%; 90% CI –15.0, –0.75; *P*=0.030) and ITT with pathogens populations (62/327, 19.0% vs 85/335, 25.4%; 95% CI –13.9, –1.44; *P*=0.016) (Table 2). In patients without bacteria isolated at baseline, clinical failure rates were similar between treatment groups (moxifloxacin, 76/350, 21.7%; amoxicillin/clavulanic acid 61/340, 17.9%; *P*=0.120).

In the ITT population, time to clinical failure was similar in both treatment arms (Figure 2a). In the ITT with pathogens population, time to clinical failure was significantly longer for moxifloxacin vs amoxicillin/clavulanic acid (*P*=0.014) (Figures 2b). Failure rates were similar at end of therapy (EOT) (moxifloxacin 27/327, 8.3% vs amoxicillin clavulanic acid 33/335, 9.9%) with an increasing divergence in favour of moxifloxacin

at 4 weeks post-therapy (44/327, 13.5% vs 64/335, 19.1%) and 8 weeks post-therapy (62/327, 19.0% vs 85/335, 25.4%).

Efficacy by subgroups

Systemic steroid use

In all analysis populations, clinical failure rates at 8 weeks post-therapy were higher in steroid- vs non-steroid-treated patients in both treatment arms (Figures 3a, b). In steroid-treated patients, a non-significant trend for lower failure rates in favour of moxifloxacin was seen. This effect was most marked in bacteriologically positive patients (Figure 3b).

Other subgroups

No significant differences were seen in moxifloxacin and amoxicillin/clavulanic acid clinical failure rates between various subgroups (e.g. patients ≥65 years old, number of previous exacerbations) as shown in the Supplementary Material.

Baseline bacteriology and susceptibility

A total of 662 (49.0%) ITT patients had causative organisms isolated from sputum at baseline. The most common pathogens in both arms were *H. influenzae* (21.1%) followed by *P. aeruginosa* (16.8%) and *K. pneumoniae* (12.7%). *S. pneumoniae* and *M. catarrhalis* also occurred in at least 10% of patients in each arm (Table 3). The majority of isolated pathogens – except for *P. aeruginosa* – were susceptible to both drugs at baseline (Supplementary Material). In a retrospective comparison of patient characteristics for those with or without pathogens at baseline (Table 4), there were significantly more patients in the microbiologically positive group who were either >65 years, had an FEV_1 ≥30% or who had not used antibiotics in the prior three months.

Bacteriological efficacy

For the overall analysis of bacterial efficacy, eradication rates (presumed + confirmed eradications) in the PP and ITT with pathogens populations were higher for moxifloxacin vs amoxicillin/clavulanic acid (PP 70.4% vs 64.4% *P*=0.078; ITT 66.0% vs 58.8% *P*=0.026) at EOT (Table 3). Eradication rates were higher in the moxifloxacin arm during therapy, although converged with those of amoxicillin/clavulanic acid towards 8 weeks. In the ITT with pathogens population, eradication rates during therapy for moxifloxacin and amoxicillin/clavulanic acid, respectively, were 231/327 (70.6%) and 196/335 (58.5%) (*P*=0.0004). At 4 weeks post-therapy, eradication rates were 196/327 (59.9%) and 193/335 (57.6%) (*P*=0.35), while at 8 weeks post-therapy they were 194/327 (59.3%) and 183/335 (54.6%) (*P*=0.088). Similar results were seen

in the PP with pathogens population (data not shown). Individual pathogen eradication rates at EOT are shown in Table 3. Development of resistance or MIC increases while on therapy was rare and had no impact on outcome for either therapy (data not shown).

Overall, eradication rates at EOT were similar between steroid and non-steroid users (150/245, 61.2% vs 263/417, 63.1%; *P*=0.655) in the ITT with pathogens population. There was no difference between the two antibiotics at EOT in bacteriological eradication rates in steroid-treated patients (moxifloxacin 77/126, 61.1%; amoxicillin/clavulanic acid 73/119, 61.3%), but in non-steroid-treated patients eradication rates were higher for moxifloxacin (moxifloxacin 139/201, 69.2%, amoxicillin/clavulanic acid 124/216, 57.4% *P*=0.001).

Association of bacterial eradication rates at EOT to clinical efficacy at primary endpoint (8 weeks post-therapy)

In the overall ITT with pathogens population, clinical cure rates at 8 weeks were higher in patients with confirmed + presumed eradication (329/413, 79.7%) vs those with persistence + presumed persistence + superinfection at EOT (123/225, 54.7% *P*<0.0001). Similar results were seen within each treatment group (moxifloxacin 182/216, 84.3% vs 55/103, 53.4%; *P*<0.0001; amoxicillin/clavulanic acid, 147/197, 74.6% VS 68/122, *P*=0.0007). When considering patients with confirmed bacterial eradication at EOT, clinical cure rates were significantly higher at 8 weeks post-therapy than those with confirmed bacterial persistence or superinfection (149/194, 76.8% vs 123/198, 62.1%; *P*=0.0014). In the moxifloxacin arm, 86/107 (80.4%) patients with confirmed eradication at EOT had clinical cure at 8 weeks, compared with 55/90 (61.1%) who had persistence/superinfection (*P*=0.003). In the amoxicillin/clavulanic acid arm, 63/87 (72.4%) of patients with confirmed eradication had clinical cure at 8 weeks, vs 68/108 (63.0%) who had persistence/superinfection (*P*=0.150).

Spirometry and patient-reported outcomes

In both treatment arms of the ITT population, absolute FEV_1 improved significantly from enrolment (moxifloxacin 0.982 L, amoxicillin/clavulanic acid 0.969 L) to 8 weeks post-therapy (moxifloxacin 1.216 L, amoxicillin/clavulanic acid 1.150 L, *P*<0.0001 for both arms). There was a trend for greater improvements at all time points in the moxifloxacin vs the amoxicillin/clavulanic acid arm for both changes in absolute

(moxifloxacin 0.207 L vs amoxicillin/clavulanic acid 0.177 L) and %predicted FEV_1 (moxifloxacin 8.13 vs amoxicillin/clavulanic acid 7.07) (see Supplementary Material). A gradual but marked improvement was seen in SGRQ scores in both treatment arms from baseline to 8 weeks post-therapy. No significant differences were seen between the treatment arms at the primary endpoint (moxifloxacin –20.5, amoxicillin/clavulanic acid –20.4). Mean changes in AECB-SS scores at 8 weeks post-therapy (moxifloxacin –1.36, amoxicillin/clavulanic acid –1.42) did not differ between treatments (see Supplementary Material).

Safety

Both treatments were equally well-tolerated with no unexpected adverse events (AEs) seen in either arm. A total of 220 moxifloxacin- and 218 amoxicillin/clavulanic acid-treated patients experienced an AE (Table 5) with 1.8% and 1.3% of patients in the two arms prematurely discontinuing treatment due to an AE.

The most commonly occurring drug-related AEs are shown in Table 5; gastrointestinal-related events were most frequently reported, although occurred in <2% of patients in either arm. In the amoxicillin/clavulanic acid arm there was one report of *Clostridium difficile*-related disease and one of *C. difficile*/pseudomembranous colitis. Serious drug-related adverse events were rare: in the moxifloxacin arm, four patients experienced one event each (anaphylactic reaction, bronchitis, gastroenteritis and tachyarrhythmia) while in the amoxicillin/clavulanic acid arm, two patients each experienced one event (allergic dermatitis and radial nerve palsy). The tachyarrhythmia occurred in an elderly (74 years) woman and resolved with adjunctive therapy**;** the study drug treatment was not discontinued. There were three AE-related deaths in each arm but none were considered to be treatment-related. All-cause hospitalisation rates were similar across arms (ITT population: moxifloxacin 41/677, 6.1%; amoxicillin/clavulanic acid, 47/675, 7.0%; *P*=0.48).

Discussion

The MAESTRAL study met its primary endpoint and demonstrated the non-inferiority of moxifloxacin to amoxicillin/clavulanic acid in the treatment of exacerbations of moderate-to-severe COPD. Moxifloxacin was superior to amoxicillin/clavulanic acid with respect to reducing clinical failure rates at the 8 week time point in patients with a

bacteriologically confirmed exacerbation. At the EOT visit the overall bacterial eradication rate was significantly higher for moxifloxacin than for amoxicillin/clavulanic acid. Higher bacteriological efficacy for moxifloxacin vs amoxicillin/clavulanic acid was due to *H. influenzae*, the most common pathogen. There was a significant relationship between the bacterial eradication at EOT and the rate of clinical cure at 8 weeks in the overall population and in patients treated with moxifloxacin but not in those treated with amoxicillin/clavulanic acid. Overall, both treatments were well-tolerated and in this elderly population of outpatients with multiple co-morbidities and co-medications there were no reports of tendonitis, or drug-related hepatic adverse events.

MAESTRAL enrolled a cohort of outpatients with Anthonisen type 1 exacerbations of moderate-to-severe COPD and treated them with one of two antibiotics recommended in this patient group: moxifloxacin and amoxicillin/clavulanic acid [14,15]. A large proportion of the patients had risk factors for poor outcomes [23]. A data review committee reviewed all results designated as clinical failures and indeterminate outcomes. Such an approach improves the accuracy and consistency of results [24]. Clinical failure rates at 8 weeks for both therapies were about 20% in the main analysis populations, similar to that seen in previous studies that have stratified by disease severity [25] or used longer-terms endpoints [26]. As shown by the survival curves, treatment failure rates were low in both treatment arms at EOT; there was short period of accelerated relapse soon after stopping antibiotic treatment; then a steady relapse rate between 2 and 4 weeks, with a slower decline up to 8 weeks. This indicates that a time period of 4 weeks or greater may be more reliable than traditional endpoints to assess the differences in efficacy of antibiotic treatment in AECOPD. There were no differences between moxifloxacin and amoxicillin/clavulanic acid in the relapse rate during the 8-week follow up period in the overall population. However, there were significantly fewer treatment failures in patients with a confirmed bacterial AECOPD treated with moxifloxacin .

The MAESTRAL population was screened to include only patients most likely to have a bacterial AECOPD, and bacterial isolation rates (48%) were comparable to a number of studies looking at similar populations [27, 28]. The pathogen profile in the MAESTRAL study was as expected in this population of older patients with underlying moderate-to-very severe airway obstruction [29, 30]. In terms of bacteriological eradication rates at EOT, moxifloxacin was more effective overall (P<0.03) and against *H. influenzae,* as would be expected from previous studies [31]. The

effectiveness of moxifloxacin in confirmed bacterial AECOPD was not explained by a higher activity against *P. aeruginosa* since eradication of this pathogen was similar in the two groups (Table 3). The higher bacteriological eradication rates in the moxifloxacin arm may have been responsible for driving the superiority of moxifloxacin at 8 weeks post-therapy in bacteriologically positive patients. A key observation in the MAESTRAL study was that overall, and in the moxifloxacin group, patients who achieved eradication of the primary pathogen at EOT had significantly higher cure rates at 8 weeks post-therapy vs patients with persistence or superinfection (overall *P*=0.001; moxifloxacin *P*=0.003). Although similar results have previously been seen at the end of therapy in short-term studies [32], the importance of bacterial eradication in continued clinical cure has not been previously reported. These results underscore the importance of bacterial eradication in preventing relapse [10,33], and support the hypothesis of continued inflammation caused by persistent infection as an underlying mechanism for relapse and recurrent exacerbations [34].

Although the importance of stratifying patients by oral steroid use to avoid bias in results has been emphasised previously [19] its application remains relatively rare in antibiotic trials of AECOPD. In the current study, 35% of patients received systemic steroid therapy, a higher number compared with that seen in previous studies (16–21%) [35,36]. Steroid use was more common in South America and Europe vs Asia Pacific, likely reflecting different therapeutic practices. The MAESTRAL analysis stratified patients by systemic steroid use, allowing identification of differences in outcomes for steroid vs non-steroid treated patients. In both treatment groups, clinical failure rates were higher in steroid vs non-steroid treated patients, as seen previously [37]. The severity of the underlying COPD based on FEV_1 measurement at enrolment was greater in the patients who received systemic steroids vs those who did not, and a greater proportion of steroid vs non-steroid patients qualified as having very severe COPD. A retrospective analysis of data showed that systemic steroid-treated patients had a longer respiratory history and more breathlessness with tachycardia. Therefore, patients treated with oral steroids had more severe disease, and as a group did less well despite steroid and antibiotic treatment. In patients receiving systemic steroids, there was trend towards a lower failure rate for moxifloxacin vs amoxicillin/clavulanic acid.

During the design of the MAESTRAL study, ethics committees expressed a strongly held view that the option to use steroids must be made available to physicians. While

the role of steroids in addition to antibiotics in patients severe enough to be hospitalised for exacerbations or to require emergency room evaluation is supported by clinical evidence, their use in outpatient office practice settings has not been as systematically investigated [35, 38, 39]. The retrospective analysis described above showed that oral steroids were appropriately prescribed in more serious exacerbations.

A number of patient characteristics were associated with pathogen presence at baseline: age ≥65 years, no recent antibiotic use and FEV_1 ≥30%. However, the differences were small and unlikely to be clinically useful in identifying patients with pathogens. Although the macroscopic appearance of the sputum at baseline was checked against a colour chart for all patients by the investigators, a significant number of sputum samples did not grow any bacteria. Sputum colour assessed by colour chart is a strong predictor of bacterial aetiology of exacerbations, but its excellent diagnostic yield observed in unicentre studies drops dramatically in multicentre trials probably due to the subjective assessment despite the colour chart [40–42]. Since approximately half of patients in the present study produced sputum which did not contain bacteria on culture, it seems likely that a significant proportion of patients had another cause for their exacerbation. While molecular diagnosis of infection [43] or the use of biomarkers could be used at the point of care to help identify these patients, identification from clinical characteristics alone remains challenging.

Choosing the most appropriate antibiotic for an AECOPD patient is dependent on a number of factors including severity of COPD, underlying risk factors for poor outcome (e.g. older age, low FEV_1, a high number of previous exacerbation, and comorbid conditions [23]) and previous antibiotic use [13,14,44]. Current guidelines differ in their antibiotic recommendations for antibiotic choice for outpatient AECOPD. While the GOLD [14] and Canadian [15] guidelines use the risk factors above to identify complicated patients, and recommend treatment with amoxicillin/clavulanate or fluoroquinolones such as moxifloxacin in these patients, others [13,44,45] recommend initial treatment with amoxicillin, tetracycline or doxycycline in all outpatients. Several studies have compared the efficacy of the various antibiotics recommended in clinical guidelines. In the MOSAIC study, which compared moxifloxacin with a basket of comparators (amoxicillin, clarithromycin or cefuroxime), moxifloxacin resulted in

superior clinical cure rates overall, as well as higher bacteriological success rates in patients with a confirmed bacterial pathogen [19]. Furthermore, moxifloxacin-treated patients were significantly less likely than those treated with a comparator to experience treatment failure, a new exacerbation or require any further antibiotic treatment within 5 months of the end of treatment. A number of other clinical trials and meta-analyses have also shown better outcomes for alternative vs first-line treatments [12, 36, 46, 47]. Among these, two studies identified quinolones as effective therapy options in terms of increasing treatment success vs first-line therapies [12] and reducing relapse rates [47]. The relatively low failure rates (approximately 20%) in the MAESTRAL study suggest that treatment with broader spectrum drugs, such as moxifloxacin or amoxicillin/clavulanic acid, is appropriate in this group of patients with moderate-to-severe AECOPD managed outside the hospital.

As with all clinical studies, there are limitations to the MAESTRAL trial. The study design included stratification by systemic steroid use, but not other respiratory co-medications as this would have significantly increased the complexity of the study. However, as the number of patients receiving respiratory co-medications was well-balanced between the moxifloxacin and amoxicillin/clavulanic acid groups, it is unlikely that respiratory co-medications had a disproportionate effect on efficacy outcomes in either treatment arm. The changes recorded by both PRO instruments during the study were substantial but did not differentiate between the two antibiotics. While the SGRQ is a widely used tool for measuring health status in patients with COPD, it is designed to measure health status during the stable phase of the disease, rather than during an exacerbation [48]. Therefore, its results must be interpreted with caution [49]. Similarly, the AECB-SS questionnaire, which measures symptoms in exacerbations, has not yet been validated. Investigators' decisions about failure were considered by the DRC, and this assessment showed that clinical judgment was, at times, variable. We believe that this review process, which, in some cases, involved going back to the investigator with questions, did improve the validity of our results. A further possible limitation is the large number of countries involved in the study which resulted in only a small number of cases in some countries. Nevertheless, further analysis of the data revealed similar failure rates for countries enrolling either small or large numbers of patients, which suggests no selection bias. The dose of amoxicillin/clavulanic acid used in the current study (875/125 mg bid) is widely used in

many clinical trials. While the 625 mg t.d.s. dose of amoxicillin has a better time above MIC pharmacokinetic/pharmacodynamic (PK/PD) profile [50], there is no established superiority for this dose versus the 875 mg b.d. dose administered in the current study. Furthermore, tolerability is greater with b.d. than t.d.s. dosing [21, 51].

The MAESTRAL study met its primary endpoint with moxifloxacin showing non-inferiority to amoxicillin/clavulanic acid. The good efficacy and tolerability of both drugs confirms their position as recommended treatments for exacerbations for outpatients with moderate-to-severe AECOPD with a suspected bacterial aetiology [14,15,34]. The strong correlation between bacterial eradication at EOT and continued clinical cure up to 8 weeks past the exacerbation emphasises the importance of antibiotic treatment in AECOPD. The higher bacterial eradication rates in the moxifloxacin arm may explain the superior outcomes in patients with a bacteriologically confirmed infection, suggesting this treatment could be a preferred option in patients where bacterial infection is most likely. These differences were most evident at the 4 and 8 week post-therapy timepoints, indicating that prolonged endpoints may be more useful for discerning clinically relevant differences between antibiotics, a factor that should be taken into account in the design of future trials. The differences between steroid and non-steroid users indicate that stratification is an important aspect of trial design and deserves further study. It is hoped that the outcomes of MAESTRAL will lead to further work to define clinical criteria and/or biomarkers to help clinicians identify both the most appropriate patients for antibiotic therapy and the most appropriate antibiotic therapy for individual AECOPD patients.

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REFERENCES

1 Miravitlles M, Ferrer M, Pont A, Zalacain R, Alvarez-Sala JL, Masa JF, Verea H, Murio C, Ros F, Vidal R, for the IMPAC study group. Exacerbations impair quality of life in patients with chronic obstructive pulmonary disease. A two-year follow-up study. *Thorax* 2004; 59: 387–395.

2 Sapey E, Stockley RA. COPD exacerbations. 2: aetiology. *Thorax* 2006; 61: 250–258.

3 Wedzicha JA, Donaldson GC. Exacerbations of chronic obstructive pulmonary disease. *Respir Care* 2003; 48: 1204–1213.

4 Wilkinson T, Wedzicha JA. Strategies for improving outcomes of COPD exacerbations. *Int J Chron Obstruct Pulmon Dis* 2006; 1: 335–342.

5 Blanchard AR. Treatment of acute exacerbations of COPD. *Clin Cornerstone* 2003; 5: 28–36.

6 Niewoehner DE. The impact of severe exacerbations on quality of life and the clinical course of chronic obstructive pulmonary disease. *Am J Med* 2006; 119: S38–S45.

7 Sethi S. Antibiotics in acute exacerbations of chronic bronchitis. *Expert Rev Anti Infect Ther* 2010; 8: 405–417.

8 Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847–852.

9 Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW, Vestbo J, Knobil K, Yates JC, Calverley PM. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008; 15: 332–338.

10 White AJ, Gompertz S, Bayley DL, Hill SL, O'Brien C, Unsal I, Stockley RA. Resolution of bronchial inflammation is related to bacterial eradication following treatment of exacerbations of chronic bronchitis. *Thorax* 2003; 58: 680–685.

11 Dever LL, Shashikumar K, Johanson WG. Antibiotics in the treatment of acute exacerbations of chronic bronchitis. *Exp Opin Invest Drugs* 2002; 11: 911–925.

12 Siempos II, Dimopoulos G, Korbila IP, Manta K, Falagas ME. Macrolides, quinolones and amoxicillin/clavulanate for chronic bronchitis: a meta-analysis. *Eur Respir J* 2007; 29: 1127–1137.

13 Woodhead M, Blasi F, Ewig S, Huchon G, Ieven M, Ortqvist A, Schaberg T, Torres A, van der Heijden G, Verheij TJ; European Respiratory Society; European Society of Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; 26: 1138–1180.

14 GOLD. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2010. Available from: http://www.goldcopd.org [Date last accessed 7th May, 2011]

15 O'Donnell DE, Hernandez P, Kaplan A, Aaron S, Bourbeau J, Marciniuk D, Balter M, Ford G, Gervais A, Lacasse Y, Maltais F, Road J, Rocker G, Sin D, Sinuff T, Voduc N. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2008 update - highlights for primary care. *Can Respir J* 2008; 15(Suppl A): 1A–8A.

16 Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106: 196–204.

17 Spencer S, Jones PW, GLOBE Study Group. Time course of recovery of health status following an infective exacerbation of chronic bronchitis. *Thorax* 2003; 58: 589–593.

18 Hurst JR, Donaldson GC, Quint JK, Goldring JJP, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009; 179: 369–374.

19 Wilson R, Anzueto A, Miravitlles M, Arvis P, Faragó G, Haverstock D, Trajanovic M, Sethi S. A novel study design for antibiotic trials in acute exacerbations of COPD: MAESTRAL methodology. *Int J COPD* 2011; in press.

20 Wilson R, Allegra L, Huchon G, Izquierdo J-L, Jones P, Schaberg T, Sagnier PP and the MOSAIC Study Group. Short and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute exacerbations of chronic bronchitis. *Chest* 2004; 125: 953–964.

21 Calver AD, Walsh NS, Quinn PF, Baran C, Lonergan V, Singh KP, Orzolek WS and the Lower Respiratory Tract Infection Collaborative Study Group. Dosing of amoxicillin/clavulanate given every 12 hours is as effective as dosing every 8 hours for treatment of lower respiratory tract infection. *Clin Infect Dis* 1997; 24 :570–4

22 Clinical Laboratory Standards Institute. CLSI document MA07-A8. Wayne, PA, 2009.

23 Wilson R, Jones P, Schaberg T, Arvis P, Duprat-Lomon I, Sagnier PP and for the Mosaic Study Group. Antibiotic treatment and factors influencing short and long term outcomes of acute exacerbations of chronic bronchitis. *Thorax* 2006; 61: 337–342.

24 Aaron SD, Fergusson D, Marks GB, Suissa S, Vandemheen KL, Doucette S, Maltais F, Bourbeau JF, Goldstein RS, Balter M, O'Donnell D, Fitzgerald M; Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. Counting, analysing and reporting exacerbations of COPD in randomised controlled trials. *Thorax* 2008; 63: 122–128. Epub 2007 Aug 16.

25 Adams SG, Melo J, Luther M, Anzueto A. Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. *Chest* 2000; 117: 1345–1352.

26 Petitpretz P, Choné C, Trémolières F; Investigator Study Group. Levofloxacin 500 mg once daily versus cefuroxime 250 mg twice daily in patients with acute exacerbations of chronic obstructive bronchitis: clinical efficacy and exacerbation-free interval. *Int J Antimicrob Agents* 2007; 30: 52–59.

27 Nalepa P, Dobryniewska M, Busman T, Notario G. Short-course therapy of acute bacterial exacerbation of chronic bronchitis: a double-blind, randomized, multicenter comparison of extended-release versus immediate-release clarithromycin. *Curr Med Res Opin* 2003; 19: 411–420.

28 Burley CJ, Masterton RG, Lovell DP. Indicators of bacterial infection in patients with acute exacerbation of chronic bronchitis for application in clinical trials of antibacterial drugs. *J Infect* 2007; 55: 226–232.

29 Miravitlles M, Espinosa C, Fernández-Laso E, Martos JA, Maldonado JA, Gallego M and Study Group of Bacterial Infection in COPD. Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. *Chest* 1999; 116: 40–46.

30 Albertson TE, Louie S, Chan AL. The diagnosis and treatment of elderly patients with acute exacerbation of chronic obstructive pulmonary disease and chronic bronchitis. *J Am Geriatr Soc* 2010; 58: 570–579.

31 Miravitlles M. Moxifloxacin in the management of exacerbations of chronic bronchitis and COPD. *Int J Chron Obstruct Pulmon Dis* 2007; 2: 191–204.

32 Alvarez-Sala JL, Kardos P, Martínez-Beltrán J, Coronel P, Aguilar L. Clinical and bacteriological efficacy in treatment of acute exacerbations of chronic bronchitis with cefditoren-pivoxil versus cefuroxime-axetil. *Antimicrob Agents Chemother* 2006; 50: 1762−1767.

33 Chodosh S. Clinical significance of the infection-free interval in the management of acute bacterial exacerbations of chronic bronchitis. *Chest* 2005; 127: 2231–2236.

34 Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 2355–2365.

35 Aaron SD, Vandemheen KL, Hebert P, Dales R, Stiell IG, Ahuja J, Dickinson G, Brison R, Rowe BH, Dreyer J, Yetisir E, Cass D, Wells G. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med* 2003; 348: 2618–2625.

36 Daniels JM, Snijders D, de Graaff CS, Vlaspolder F, Jansen HM, Boersma WG. Antibiotics in addition to systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; 181: 150–157.

37 Roede BM, Bresser P, Bindels PJ, Kok A, Prins M, ter Riet G, Geskus RB, Herings RM, Prins JM. Antibiotic treatment is associated with reduced risk of a subsequent exacerbation in obstructive lung disease: an historical population based cohort study. *Thorax* 2008; 63: 968–973.

38 Niewoehner DE. Clinical Practice. Outpatient management of severe COPD. *N Engl J Med* 2010; 362: 1407−1416.

39 Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, Anderson J, Maden C; TRial of Inhaled STeroids ANd long-acting beta2 agonists study group. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; 361: 449–456.

40 Allegra L, Blasi F, Diano P, Cosentini R, Tarsia P, Confalonieri M, Dimakou K, Valenti V. Sputum color as a marker of acute bacterial exacerbations of chronic obstructive pulmonary disease. *Respir Med* 2005; 99: 742–747.

41 Brusse-Keizer MG, Grotenhuis AJ, Kerstjens HA, Telgen MC, van der Palen J, Hendrix MG, van der Valk PD. Relation of sputum colour to bacterial load in acute exacerbations of COPD. *Respir Med* 2009; 103: 601–606.

42 Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest* 2000; 117: 1638–1645.

43 Sethi S. Molecular diagnosis of respiratory tract infection in acute exacerbations of chronic obstructive pulmonary disease. *Clin Infect Dis* 2011; 52(Suppl 4): S290–S295.

44 Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932–946.

45 Qaseem A, Snow V, Shekelle P, Sherif K, Wilt TJ, Weinberger S, Owens DK; Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2007; 147: 633–638.

46 Destache CJ, Dewan N, O'Donohue WJ, Campbell JC, Angelillo VA. Clinical and economic considerations in the treatment of acute exacerbations of chronic bronchitis. *J Antimicrob* Chemother 1999; 43(Suppl A): 107–113.

47 Dimopoulos G, Siempos II, Korbila JP, Manta KG, Falagas ME. Comparison of first-line with second-line antibiotics for acute exacerbations of chronic bronchitis: a metaanalysis of randomized controlled trials. *Chest* 2007; 132: 447–455.

48 Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; 145: 1321–1327.

49 Doll H, Duprat-Lomon I, Ammerman E, Sagnier PP. Validity of the St George's respiratory questionnaire at acute exacerbation of chronic bronchitis: comparison with the Nottingham health profile. *Qual Life Res* 2003; 12: 117–132.

50 Bax R. Development of a twice daily dosing regimen of amoxicillin/clavulanate. *Int J Antimicrob Agents* 2007; 30 Suppl 2: S118–S121.

51 Geddes AM, Klugman KP, Rolinson GN. Introduction: historical perspective and development of amoxicillin/clavulanate. *Int J Antimicrob Agents* 2007; 30 Suppl 2: S109–12.

TABLE 1 Baseline demographics and patient characteristics in the per-protocol population

Characteristic	Moxifloxacin (N=538)	Amoxicillin/ clavulanic acid (N=518)
Geographic region, n (%)		
Asia/Pacific	162 (30)	160 (31)
Europe	188 (35)	187 (36)
South Africa	24 (5)	11 (2)
Latin America	155 (29)	155 (30)
Canada	9 (2)	5 (1)
Male sex, n (%)	425 (79)	408 (79)
Race, n (%)		
Caucasian	326 (61)	310 (60)
Asian	166 (31)	163 (31)
Other	46 (9)	45 (9)
Age (years), mean ± SD	69.6 ± 6.8	69.3 ± 6.3
Range	59 - 93	60 - 88
≥ 65 yrs, n (%)	389 (72)	378 (73)
BMI (kg/m^2), mean ± SD	25.0 ± 5.4	24.7 ± 4.9
Current smokers, n (%)	113 (24)	121 (23)
Co-existing illnesses, n (%)	417 (78)	419 (81)
Coronary artery disease	63 (12)	43 (8)
Congestive heart failure	25 (5)	25 (5)
Peripheral artery disease	11 (2)	4 (1)
Renal dysfunction	15 (3)	15 (3)
Liver dysfunction	8 (1)	11 (2)
Diabetes mellitus	50 (9)	53 (10)
Any respiratory comedication	495 (92)	475 (92)
Short or long-acting beta-2-agonists	292 (54)	276 (53)
Inhaled steroids[†]	283 (53)	275 (53)
Ipratropium or tiotropium	241 (45)	226 (44)
Xanthine derivatives	176 (33)	163 (32)
Previous antimicrobial use[‡], n (%)	190 (35)	174 (34)
Systemic steroid use, n (%)	182 (34)	189 (36)
Cumulative dose (mg), mean (range)	183 (50–350)	180 (50–350)
Duration of steroid therapy	5	5

(days), median		
Lung function at enrolment *All patients* FEV, % predicted, mean ± SD FEV_1 (L), mean ± SD FEV_1 <30%, n (%) *Systemic steroid-treated* FEV, % predicted (L), mean ± SD FEV_1 (L), mean ± SD FEV_1 <30%, n (%)	 39.280 ±11.621 0.982 ± 0.369 139 (26) 36.479 ±11.704 0.928 ± 0.339 54 (30)	 39.186 ±11.360 0.970 ± 352 129 (25) 36.769 ±11.007 0.920 ± 0.345 57 (30)
Exacerbations in previous year Mean ± SD ≥3	 2.5 ± 1.1 165 (31)	 2.5 ± 0.9 152 (29)
Time since last exacerbation (days), mean ± SD	109.6 ± 65.8	105.0 ± 62.0
Colour of sputum, n (%)[§] Yellow, Green Rust	 327 (61) 194 (36) 17 (3)	 331 (64) 174 (34) 13 (3)
AECB-SS, mean ± SD **SGRQ, mean ± SD**	2.2 (0.6) 64.9 (18.1)	2.2 (0.7) 63.5 (18.9)

[†]Includes comination therapy (steroid plus bronchodilators)
[‡]Any antimicrobial given for any indication between 30 and 90 days prior to enrolment
[§]Identified by colour chart
BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; AECB-SS: Acute Exacerbation of Chronic Bronchitis Symptom Score; SGRQ: St George's Respiratory Questionnaire

TABLE 2 Clinical failure rates at 8-week post-therapy

Population	Moxifloxacin n/N (%)	Amoxicillin/ clavulanic acid n/N (%)	95% CI[†]	*P*-value
Per-protocol	111/538 (20.6)	114/518 (22.0)	–5.89, 3.83	n/a[‡]
Intent-to-treat	138/677 (20.4)	146/675 (21.6)	–5.50, 3.03	0.571
Per-protocol with pathogens	50/260 (19.2)	68/261 (26.1)	–15.0, –0.75	0.030
Intent-to-treat with pathogens	62/327 (19.0)	85/335 (25.4)	–13.9, –1.44	0.016

n/N: number with clinical failure/total number in population
Failures and relapses are included in the failure rate calculation; missing/indeterminates counted as non-clinical failures in the intent-to-treat populations
n/a: not applicable
[†]Stratified by steroid use and geographical region
[‡]Non-inferiority margin 6%; primary analysis designed for non-inferiority only, no superiority tests carried out

TABLE 3 Most commonly isolated pathogens at baseline and bacteriological eradication rates at end of therapy

	Bacteriological eradication		**95% CI[†]**
	Moxifloxacin n/N (%)	**Amoxicillin/ clavulanic acid n/N (%)**	
Population	**Overall**		
Per protocol with pathogens	183/260 (70.4)	168/261 (64.4)	–0.7, 15.2[‡]
Intent-to-treat with pathogens	216/327 (66.0)	197/335 (58.8)	1.1, 15.7[§]
Pathogen	**By pathogen[¶]**		
Haemophilus influenzae	58/65 (89.2)	50/75 (66.7)	8.1, 37.1
Pseudomonas aeruginosa	31/57 (54.5)	32/54 (59.3)	–25.1, 15.3
Streptococcus pneumoniae	44/49 (89.8)	33/38 (86.8)	–13.1, 19.0
Klebsiella pneumoniae	21/36 (58.3)	19/48 (39.6)	–4.9, 42.4
Moraxella catarrhalis	30/36 (83.3)	37/43 (86.0)	–21.2, 15.8
Staphylococcus aureus	20/23 (87.0)	16/20 (75.0)	–20.0, 33.9
Escherichia coli	14/21 (66.7)	11/16 (68.8)	–38.0, 33.8
Serratia marcescens	10/14 (71.4)	9/14 (62.3)	34.5, 48.8
Enterobacter cloacae	9/11 (81.8)	7/8 (87.5)	–48.8, 37.4

Enterobacter aerogenes	5/8 (62.5)	6/8 (75.0)	–70.0, 45.0
Klebsiella oxytoca	9/11 (81.8)	2/4 (50.0)	–39.3, 100
Proteus mirabilis	1/4 (25.0)	6/9 (66.7)	–100, 28.8

n/N: bacteriological eradication + presumed eradication/total number of patients or organisms; n/a: not applicable

† 95% confidence levels for differences in organism eradication rates were generated using a normal approximation to the binomial distribution, with a continuity correction

‡ *P*=0.078

§ *P*=0.026

¶ ITT with pathogens population

TABLE 4 Characteristics at enrolment of patients (for which comparisons led to p-values <0.10) with and without pathogens

Characteristic	ITT with pathogens N=662	ITT without pathogens N=690	*P*-value[†]
Age group (years), n %			0.0003
≥75	167 (25.2)	147 (22.9)	
<75	495 (74.8)	495 (77.1)	
Alcohol use			0.046
Abstinent	415 (62.7)	453 (65.8)	
Light consumption	222 (33.5)	196 (28.4)	
Moderate consumption	25 (3.8)	40 (5.8)	
Sex, n %			0.064
Male	542 (81.9)	537 (77.9)	
Female	120 (18.1)	152 (22.0)	
FEV_1 at enrolment, n %			0.021
<30%	149 (22.6)	190 (27.6)	
≥30%	510 (77.4)	498 (72.4)	
Diabetes			0.095
Yes	80 (12.1)	64 (9.3)	
No	582 (87.9)	626 (90.7)	
Cardiopulmonary disease			0.011
Yes	92 (13.9)	65 (9.4)	
No	570 (86.1)	625 (90.6)	
Respiratory disease			0.070
Yes	134 (20.2)	168 (24.3)	
No	528 (79.8)	522 (75.7)	
History of respiratory failure			0.035
Yes	59 (8.9)	86 (12.5)	
No	603 (91.1)	603 (87.5)	
Short-acting anticholinergics			0.015
Yes	95 (14.3)	69 (10.0)	
No	567 (85.7)	621 (90.0)	
Short-acting bronchodilator			0.080
Yes	153 (23.1)	188 (27.2)	
No	509 (76.9)	502 (72.8)	
Previous antibiotic use,[‡] n %			0.021
Yes	206 (31.1)	256 (37.1)	
No	456 (68.9)	434 (62.9)	
Exacerbation in last 3 months			0.069
Yes	335 (50.6)	315 (45.6)	
No	327 (49.4)	375 (54.3)	
Chest discomfort at baseline			0.020
Absent	551 (83.6)	604 (88.0)	
Present	108 (16.4)	82 (12.0)	
Wheeze at baseline			0.047
Absent	409 (62.2)	462 (67.3)	
Present	249 (37.8)	224 (32.7)	

Sputum viscosity at baseline			0.015
Liquid	24 (3.6)	22 (3.2)	
Thick	409 (61.9)	401 (58.1)	
Very thick	84 (12.7)	67 (9.7)	
Quite thick	144 (21.8)	200 (29.0)	
Wheeze at exacerbation			0.033
Absent	109 (42.9)	145 (21.0)	
Present	552 (50.4)	544 (79.0)	
AECB-SS phlegm colour			0.021
Clear/white/grey	70 (11.9)	76 (12.2)	
Yellow	318 (54.2)	382 (61.1)	
Green/brown	199 (33.9)	167 (26.7)	
AECB-SS at exacerbation: Disturbances in daily activities			0.089
Not at all/slightly	211 (35.9)	191 (30.5)	
Moderately	173 (29.4)	214 (34.1)	
A lot/extremely	204 (34.7)	222 (35.4)	

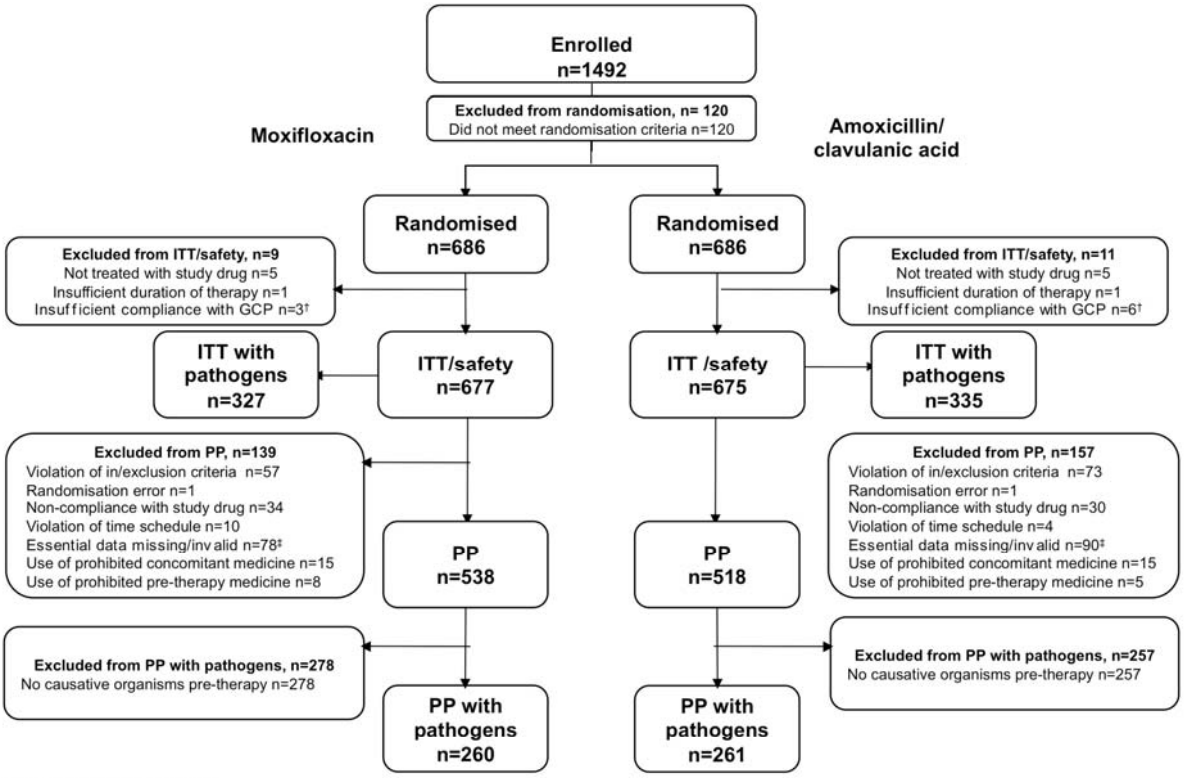
†P-values from the Wald chi-square statistic

‡Any antimicrobial given for any indication between 30 and 90 days prior to enrolment

TABLE 5 Overview of adverse events (Intent-to-treat/safety population)

Event	Moxifloxacin N=677 n (%)	Amoxicillin/clavulanic acid N=675 n (%)
Any adverse event (AE)	220 (32.5)	218 (32.3)
Drug-related AE	53 (7.8)	41 (6.1)
Diarrhoea	6 (0.9)	12 (1.8)
Nausea	10 (1.5)	4 (0.6)
Headache	5 (0.7)	3 (0.4)
Serious AE	46 (6.8)	51 (7.6)
Drug-related SAE	4 (0.6)	2 (0.3)
Premature discontinuation due to drug-related AE	12 (1.8)	9 (1.3)
AE-related deaths	3 (0.4)	3 (0.4)

N: number in safety population
n: number with adverse event
No significant differences were seen between treatments for any type of safety event (P>0.10 for all categories)



Patients could be excluded for >1 reason

PP: per protocol population (primary analysis population): patients with an acute exacerbation at enrolment who received the study drug for a minimum of 48 hours (cases of clinical failure) or received ≥80% of study medication (cases of clinical cure). All have data for clinical evaluation at 8 weeks post-therapy (except for clinical failures prior to the 8 weeks post-therapy visit) and had no protocol violations; ITT intent-to-treat/safety population: all patients randomised who received at least one dose of study drug and with one observation after initiation of study treatment
PP with pathogens population: patients drawn from the PP population and with at least one potentially pathogenic bacterium cultured from sputum provided prior to start of therapy and where a bacteriological evaluation was available during the study; ITT with pathogens population: patients valid for ITT with at least one pre-therapy potentially pathogenic bacterium.

†Data from one site (n=9 patients in total) judged to be unreliable and excluded from analysis. ‡The majority of patients with essential data missing or invalid were either lost to follow-up or consent was withdrawn (moxifloxacin , 58%; amoxicillin/clavulanic acid (56%).

Figure 1

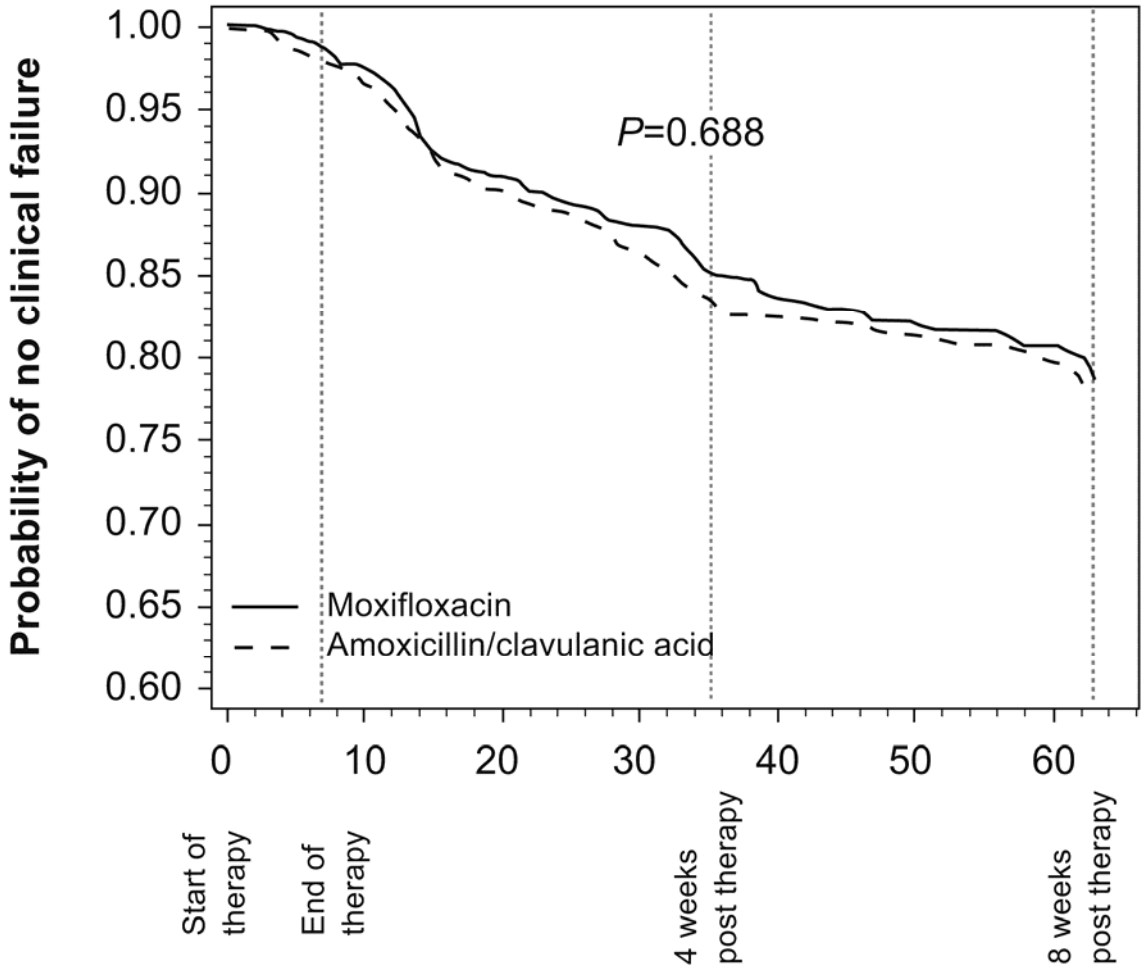

Probability of no clinical failure
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
P=0.688
Moxifloxacin
Amoxicillin/clavulanic acid
0
10
20
30
40
50
60
Start of therapy
End of therapy
4 weeks post therapy
8 weeks post therapy

Figure 2a

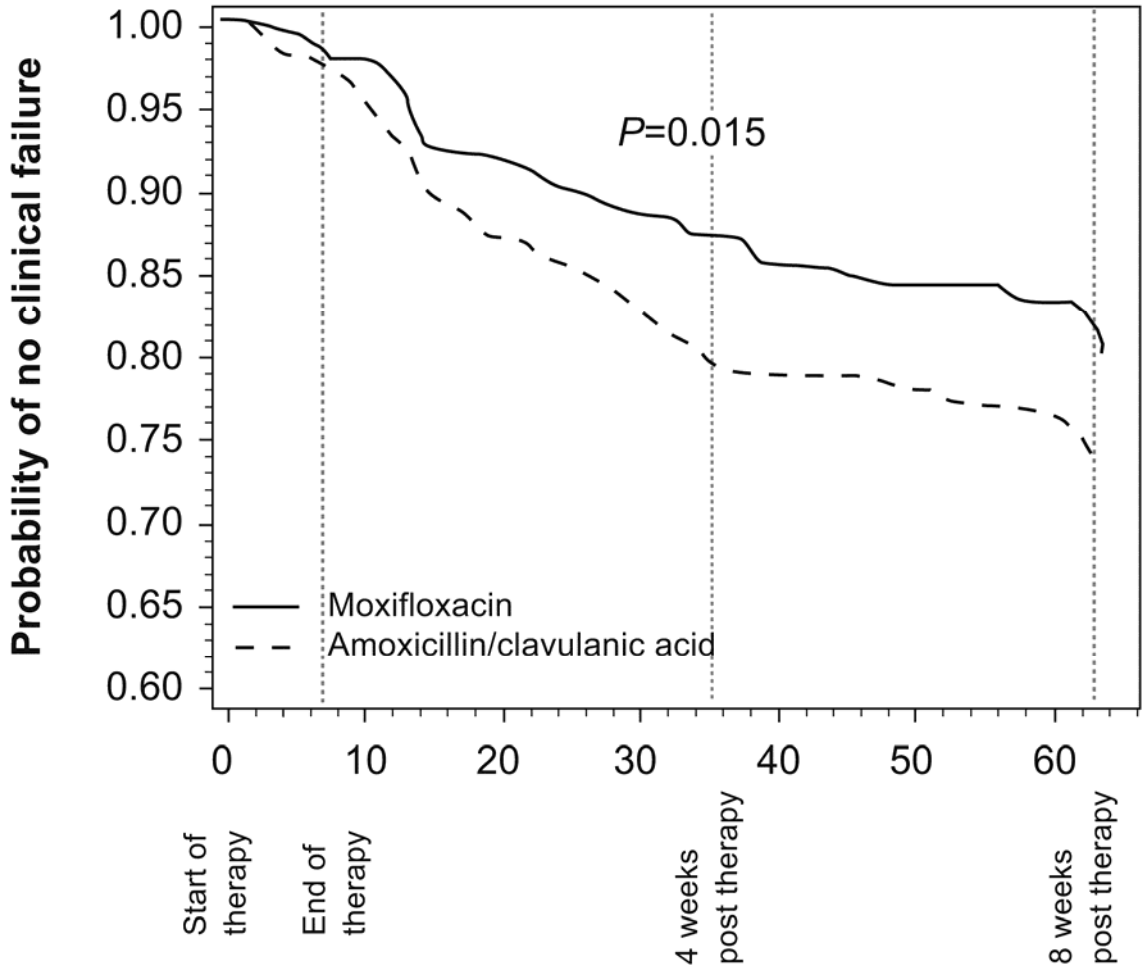

Probability of no clinical failure
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
P=0.015
Moxifloxacin
Amoxicillin/clavulanic acid
0
10
20
30
40
50
60
Start of therapy
End of therapy
4 weeks post therapy
8 weeks post therapy

Figure 2b

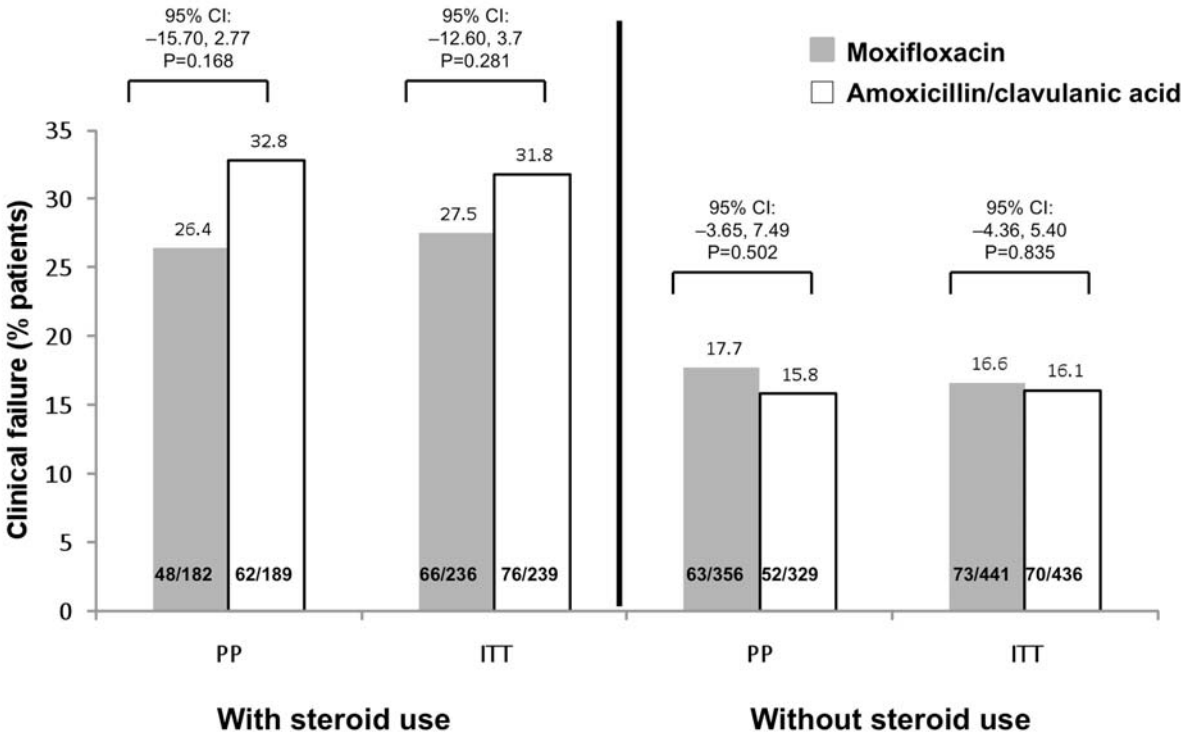

95% CI:
–15.70, 2.77
P=0.168
95% CI:
–12.60, 3.7
P=0.281
Moxifloxacin
Amoxicillin/clavulanic acid
Clinical failure (% patients)
35
30
25
20
15
10
5
0
26.4
32.8
27.5
31.8
48/182
62/189
66/236
76/239
95% CI:
–3.65, 7.49
P=0.502
95% CI:
–4.36, 5.40
P=0.835
17.7
15.8
16.6
16.1
63/356
52/329
73/441
70/436
PP
ITT
PP
ITT
With steroid use
Without steroid use

Figure 3a

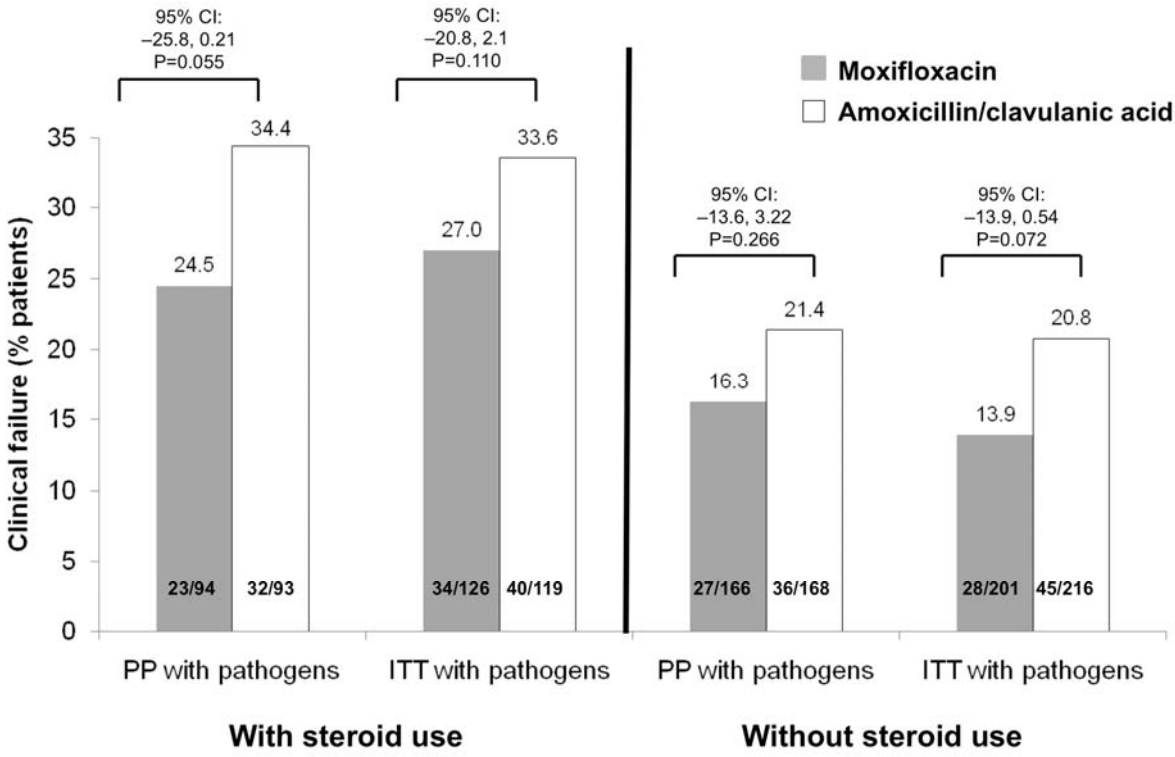

95% CI:
−25.8, 0.21
P=0.055
95% CI:
−20.8, 2.1
P=0.110
Moxifloxacin
Amoxicillin/clavulanic acid
95% CI:
−13.6, 3.22
P=0.266
95% CI:
−13.9, 0.54
P=0.072
Clinical failure (% patients)
35
30
25
20
15
10
5
0
34.4
33.6
24.5
27.0
21.4
20.8
16.3
13.9
23/94
32/93
34/126
40/119
27/166
36/168
28/201
45/216
PP with pathogens
ITT with pathogens
PP with pathogens
ITT with pathogens
With steroid use
Without steroid use

Figure 3b