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Evaluation of 5-day therapy with telithromycin, a novel ketolide antibacterial, for the treatment of tonsillopharyngitis

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ABSTRACT

A pooled analysis of two double-blind, multicentre, Phase III studies compared oral telithromycin 800 mg once-daily for 5 days with penicillin V 500 mg three-times-daily or clarithromycin 250 mg twice-daily for 10 days in the treatment of *Streptococcus pyogenes* (group A β-haemolytic streptococcus; GABHS) tonsillopharyngitis. Patients aged ≥13 years with acute GABHS tonsillopharyngitis were randomised to receive telithromycin (n = 430), penicillin (n = 197) or clarithromycin (n = 231). Clinical isolates of *S. pyogenes* (n = 590) obtained from throat swab samples on study entry were tested for their in-vitro susceptibility to telithromycin, clarithromycin and azithromycin. Telithromycin demonstrated in-vitro activity against the clinical isolates of *S. pyogenes* ($MIC_{50/90}$ 0.03/0.06 mg/L) higher than clarithromycin or azithromycin ($MIC_{50/90}$ 0.06/0.06 mg/L and 0.12/0.25 mg/L, respectively), including erythromycin-resistant strains. At the post-therapy/test of cure (TOC) visit (days 16–23), satisfactory bacteriological outcome was demonstrated for 88.3% (234/265) and 88.6% (225/254) of telithromycin- and comparator-treated patients, respectively (per-protocol population). Overall, GABHS eradication rates were 88.7% (235/265) for telithromycin and 89.0% (226/254) for comparators. The clinical cure rates at the post-therapy/TOC visit were 93.6% (248/265) and 90.9% (220/242) for telithromycin and pooled comparators, respectively. Telithromycin was generally well-tolerated. Most adverse events considered to be possibly related to study medication were gastrointestinal and of mild intensity. Discontinuations as a result of adverse events were few in both treatment groups. In conclusion, telithromycin 800 mg once-daily for 5 days was as effective as penicillin V or clarithromycin for 10 days in the treatment of GABHS tonsillopharyngitis.

Keywords Efficacy, group A β-haemolytic streptococcus, pharyngitis, *Streptococcus pyogenes*, telithromycin, tonsillitis

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INTRODUCTION

Acute tonsillopharyngitis is a common upper respiratory tract infection, and is one of the most frequent reasons for consulting a primary care physician [1]. Most acute upper respiratory tract infections are of viral origin and hence do not require treatment with antibacterials [2]. However, in the case of acute tonsillopharyngitis, *c.* 15% of episodes are caused by *Streptococcus pyogenes* (group A β-haemolytic streptococcus; GABHS), which is the most common bacterial cause of the infection [2]. While this condition is not life-threatening, morbidity such as pharyngeal pain and dysphagia necessitates rapid symptom relief through use of appropriate antibacterials [3]. Moreover, effective antibacterial therapy is recommended to reduce the spread of infection and to prevent the development of rare but significant complications, such as acute rheumatic fever [4].

Various antibacterial agents have proven efficacy against GABHS, including penicillin V, macrolides and cephalosporins [1]. Treatment for 10 days with oral penicillin V remains the treatment of choice, with macrolides such as clarithromycin and erythromycin recommended

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for patients who are allergic to penicillin [4,5]. While *S. pyogenes* remains fully susceptible to penicillin V, the utility of macrolides in penicillin-allergic patients is under threat because of the increase in macrolide resistance among *S. pyogenes* isolates in recent years [6–11].

Bacteriological and clinical failure rates in the region of 30% with penicillin V [12] have led to the development of more effective agents [4]. Non-adherence to 10-day regimens is also a common problem associated with current treatment options for tonsillopharyngitis, and has been cited as one of the factors in treatment failure [13]. Poor adherence also seems to contribute to the development and spread of antibacterial resistance [14,15]. Shortening the course of antibacterial therapy may reduce the potential for emergence of resistant strains. Indeed, there is a growing body of evidence that shorter courses of non-penicillin antibiotics are effective in the treatment of tonsillopharyngitis [16].

Telithromycin is the first of a new class of antibacterial agents developed for clinical use—the ketolides—that are structurally similar to the macrolides. In-vitro studies have shown that telithromycin has a potent and focused spectrum of antibacterial activity against respiratory pathogens, including *S. pyogenes* [17–19]. Moreover, telithromycin does not induce macrolide–lincosamide–streptogramin (MLS) resistance in *Staphylococcus aureus*, *Streptococcus pneumoniae* and *S. pyogenes* [20]. An oral regimen of telithromycin 800 mg once-daily has been shown *in vivo* to achieve and maintain plasma [21] and tissue [22,23] concentrations at or above the MIC for common respiratory pathogens, including *S. pyogenes*.

In this paper, the results of two clinical trials are combined to compare the bacteriological and clinical efficacy and safety of telithromycin 800 mg once-daily for 5 days with treatment with penicillin V 500 mg three-times-daily [24] (Study 3004) or clarithromycin 250 mg twice-daily [25] (Study 3008) for 10 days in the treatment of GABHS tonsillopharyngitis in adolescents and adult patients. These data have been presented in part previously [26].

PATIENTS AND METHODS

Two randomised (1:1), multicentre, double-blind, comparative studies were conducted in a total of 118 centres in 12 countries (Belgium, Canada, Czech Republic, Denmark, Finland, Germany, Hungary, New Zealand, South Africa, Switzerland, UK, USA). The studies were approved by local independent Ethics Committees, and were conducted in accordance with the latest revision to the Declaration of Helsinki. Written informed consent was obtained from all patients before participation in the studies.

Patients

Adolescent and adult patients aged ≥13 years were eligible for inclusion in the studies if they had clinical signs and symptoms of acute GABHS tonsillopharyngitis, which included a sore throat and one or more of the following: fever, erythema of the uvula and pharynx or tonsils, oedema of these tissues, exudates or cervical lymphadenopathy. In addition, patients needed to have either a positive test result for rapid detection of group A streptococcal antigen from a throat swab, or a positive throat culture for GABHS.

Patients were excluded if they had an infection of the deep tissues of the upper or sub-pharyngeal respiratory tract and its connecting structures; were suspected to have non-streptococcal or viral tonsillitis or pharyngitis; were suspected to be chronic streptococcal carriers or to be in an environment where reinfection was known to be occurring; had already received treatment with penicillin V for the infection; or had been treated with systemic or local antimicrobial agents within 7 days before study entry. Additional exclusion criteria, including previous or concomitant medical conditions and prohibited medications, are detailed in previous publications [24,25].

Study design

On entry to the study (day 1), patients underwent a physical examination including assessment of infection-related signs and symptoms, vital signs and 12-lead electrocardiograms (ECGs). Throat swab specimens were taken for rapid antigen detection and microbiological culture. Blood and urine samples were taken to determine laboratory safety parameters.

Patients were randomised to receive oral telithromycin 800 mg once-daily in the morning for 5 days, or a comparator antimicrobial (penicillin V 500 mg three-times-daily (Study 3004) or clarithromycin 250 mg twice-daily (Study 3008)) for 10 days. Blinding was maintained by masking the tablets in capsules and with the use of matching placebo capsules where appropriate. Following treatment with telithromycin for 5 days, patients received a matching placebo for 5 days. Adherence was assessed by counting unused returned study medication at the on-therapy and end-of-therapy visits.

Patients were reassessed in the clinic at an on-therapy visit (days 3–5), an end-of-therapy visit (days 11–13), a post-therapy therapy/test of cure (TOC) visit (days 16–23), and a late post-therapy (LPT) visit (days 31–45). Clinical signs and symptoms of infection and overall clinical status or outcome were assessed at each visit, and throat swabs for microbiological cultures, blood samples and urine samples were taken. A physical examination was also performed and vital signs were measured.

Assessments

In-vitro susceptibility testing and genotyping of clinical isolates

S. pyogenes isolates, cultured from throat swab samples obtained on entry to the study, were tested for their in-vitro susceptibility to telithromycin, clarithromycin and azithromy-

cin. Susceptibility testing was performed initially using disk diffusion methods at each participating laboratory, and subcultures of primary isolates were retested subsequently at a central laboratory (Clinical Microbiology Institute, Wilsonville, OR, USA, or GR Micro Ltd, London, UK) by disk diffusion and for MICs using National Committee for Clinical Laboratory Standards methodology [27]. The MIC distribution of telithromycin was compared with that of clarithromycin and azithromycin. Genotyping for the presence of *erm* and *mef* sequences was performed on isolates of *S. pyogenes* that were resistant to macrolides (erythromycin) [28].

Efficacy

The primary efficacy variable was bacteriological outcome at the post-therapy/TOC visit in the per-protocol (PP) population. Secondary efficacy variables were bacteriological outcome at the post-therapy/TOC visit (bacteriological modified intent-to-treat population (bmITT) population) and at the late post-therapy visit (bmITT and PP populations), and clinical outcome at the post-therapy/TOC and late post-therapy visits (modified intent-to-treat (mITT) and PP populations). Bacteriological outcome was classified as satisfactory, unsatisfactory or indeterminate at the post-therapy/TOC visit according to the following definitions.

- *Satisfactory*: the causative pathogen was absent (eradicated) or a new serotype of GABHS or bacterial strain was isolated, and the subject had no signs or symptoms of active infection (colonisation).
- *Unsatisfactory*: the causative pathogen was still present (persistence) or assumed to be present (presumed persistence); or the causative pathogen reappeared after eradication from the original site of infection (recurrence); or elimination of the initial causative pathogen was followed by replacement of a new serotype for the same organism at the same site in the presence of signs and symptoms of infection (reinfection).
- *Indeterminate*: it was not possible to categorise the microbiological response, because of incomplete microbiological data, death, withdrawal, concurrent treatment or discontinuation.

Bacteriological outcome at the late post-therapy visit was defined as: satisfactory (bacteriological response satisfactory at post-therapy/TOC visit and no recurrence or reinfection and no subsequent antimicrobial treatment for an infection at the same site); unsatisfactory (bacteriological response unsatisfactory at post-therapy/TOC visit or recurrence or reinfection or use of a new antimicrobial during follow-up); or indeterminate.

Clinical outcome was classified by the investigator as cure, failure or indeterminate, according to the following definitions:

- *Cure*: improvement, disappearance or return to preinfection state of all infection-related signs and symptoms, without the need for subsequent antimicrobial therapy.
- *Failure*: infection-related signs and symptoms remained unchanged or worsened; or additional antimicrobial therapy was initiated because of lack of clinical improvement; or development of new clinical findings consistent with active infection.
- *Indeterminate*: post-treatment information was missing or there was early discontinuation of treatment for reasons that were not drug-related.

Clinical outcome at the late post-therapy visit was defined as: cure (cure at post-therapy/TOC visit and no occurrence of a new infection); failure (failure at post-therapy/TOC visit, or signs and symptoms of a new infection at the same site or other relevant site leading to initiation of antimicrobial treatment); or indeterminate.

Safety

Adverse events, as reported by patients or noted by the investigator, were recorded throughout the study. The investigator assessed the severity of each adverse event and its relationship to study medication. Safety was evaluated on the basis of physical examination, vital signs, clinical laboratory tests and 12-lead ECG.

Statistical analyses

All randomised patients with a positive rapid streptococcal antigen test result, or positive throat culture for GABHS, who received at least one dose of study medication were included in the mITT population. The bmITT population included all patients in the mITT population with a positive culture for GABHS at the pretherapy visit.

The primary objective was to demonstrate equivalence between telithromycin and the standard comparators in terms of satisfactory bacteriological outcome at the post-therapy/TOC visit in the PP population. The PP population included all bmITT patients except those with major protocol violations. The secondary objective was to demonstrate equivalence between telithromycin and the standard comparators in terms of satisfactory bacteriological outcome at the post-therapy/TOC visit in the bmITT population. In addition, clinical efficacy was assessed for the PP population. Safety was evaluated in all patients who received at least one dose of study medication and had at least one safety assessment after the pre-therapy/entry visit.

A two-sided 95% confidence interval (CI) was constructed for the difference in bacteriological outcomes between telithromycin and comparator treatment groups.

RESULTS

In total, 860 patients were randomised to receive treatment across the two studies, 858 of whom were evaluable in the mITT population (Table 1). GABHS was isolated from 648 patients at pretherapy/entry to the study (telithromycin, n = 325; comparators, n = 323), and these formed

Table 1. Number of patients (mITT population) and treatment regimens for the two Phase III studies of telithromycin 800 mg once-daily in the treatment of patients with GABHS tonsillopharyngitis

Study	Treatment regimen			No. in mITT population
	Antibacterial	Duration (days)	Dosage	
3004	Telithromycin	5	800 mg q.d.	198
	Penicillin V	10	500 mg t.i.d.	197
3008	Telithromycin	5	800 mg q.d.	232
	Clarithromycin	10	250 mg b.i.d.	231
Combined	Telithromycin	5	–	430
	Comparators	10	–	428

mITT, modified intent-to-treat; q.d., once-daily; t.i.d., three-times-daily; b.i.d., twice-daily.

Table 2. Baseline demographics and clinical characteristics of patients treated with telithromycin (800 mg once-daily) for 5 days or a comparator antibacterial[a] for 10 days in patients with GABHS tonsillopharyngitis (mITT population)

Characteristic	Number of patients (%)	
	Telithromycin n = 430	Comparators n = 428[a]
Sex		
Male	171 (39.8)	175 (40.9)
Female	259 (60.2)	253 (59.1)
Mean age (years); range	31.6; 1–72	31.5; 13–81
Ethnicity		
White	372 (86.5)	370 (86.4)
Black	35 (8.1)	34 (7.9)
Multiracial	19 (4.4)	21 (4.9)
Other	4 (1.0)	3 (0.7)
Smoking status		
Smoker	88 (20.5)	111 (25.9)
Ex-smoker	68 (15.8)	55 (12.9)
Non-smoker	274 (63.7)	262 (61.2)
Signs and symptoms		
Fever (> 38°C)	98 (22.8)	78 (18.2)
Exudate	313 (72.8)	307 (71.7)
Cervical lymphadenopathy	395 (91.9)	396 (92.5)
No. GABHS tonsillopharyngitis episodes in 12 months		
0	320 (74.4)	327 (76.4)
1	62 (14.4)	54 (12.6)
> 1	48 (11.2)	47 (11.0)
History of ear-, nose- or throat-related surgery	37 (8.6)	39 (9.1)

[a]Penicillin V 500 mg three-times-daily or clarithromycin 250 mg twice-daily.

the bmITT population. There were 519 patients (telithromycin, n = 265; comparators, n = 254) in the PP population.

Patients receiving telithromycin or a comparator antimicrobial agent were well-matched in terms of demographics, with a mean age of 32 years (range 13–81 years), and 512 (59%) females (Table 2). The baseline disease characteristics were similar, but slightly more patients in the telithromycin group had a fever (oral temperature > 38°C) compared with those receiving comparator antibacterial agents.

For both studies, full patient adherence over the first 5 days of treatment was higher than for the total 10-day duration of therapy (telithromycin, 87.9% vs. comparators, 85.7% for the first 5 days; telithromycin, 71.9% vs. comparators, 72.9% for the total 10-day period).

In total, 76 patients discontinued the study medication (telithromycin, 37 (8.6%)/430; penicillin V, 18 (9.1%)/198; clarithromycin, 21 (9.1%)/231).

Pathogens and in-vitro susceptibility to antibacterial agents

In total, 590 isolates of *S. pyogenes* (isolated from the bmITT population) were tested for their susceptibility *in vitro* to telithromycin and the macrolides, clarithromycin and azithromycin. MIC distributions of these antibacterials are shown in Fig. 1. The activity of telithromycin against clinical isolates of *S. pyogenes* was high. Mode MIC, MIC_{50} and MIC_{90} values were 0.015 mg/L, 0.03 mg/L and 0.06 mg/L, respectively. The in-vitro activity of telithromycin against clinical isolates of *S. pyogenes* was superior to that of both clarithromycin and azithromycin. Mode MIC, MIC_{50} and MIC_{90} values were 0.06 mg/L for clarithromycin, and 0.12 mg/L, 0.12 mg/L and 0.25 mg/L, respectively, for azithromycin.

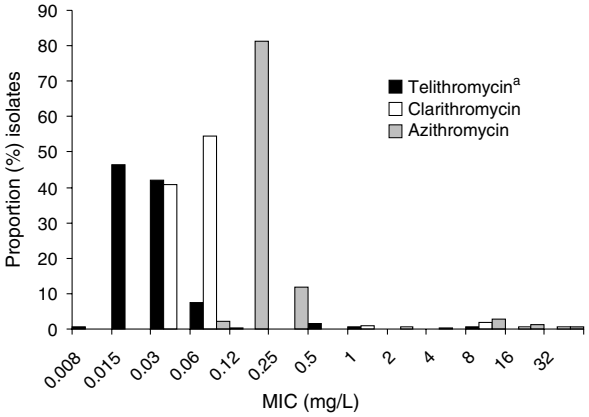

Fig. 1. MIC distributions of telithromycin, clarithromycin and azithromycin for 590 clinical isolates of *Streptococcus pyogenes*. [a]Isolates with MIC of 0.015 mg/L (Study 3004) and 0.016 mg/L (Study 3008) combined.

In this study, 28 isolates were erythromycin-resistant; genotyping of 26 isolates was performed by PCR for the presence of *erm*(B), *erm*(TR) and *mef*(A) macrolide resistance sequences. Five isolates were positive for *erm*(B) alone, nine for *erm*(TR) alone, nine for *mef*(A) alone, and three for both *erm*(B) and *mef*(A) (two erythromycin-resistant isolates were not tested). Clarithromycin and azithromycin MICs were ≥1.0 mg/L (range 1–32 mg/L) and ≥8.0 mg/L (range 8–32 mg/L), respectively, for all erythromycin-resistant isolates, irrespective of the resistance genotype. For clarithromycin and azithromycin, the MIC ranges were: *erm*(TR), 1–4 mg/L and 16–32 mg/L, respectively; *mef*(A), 4–16 mg/L and 8–16 mg/L, respectively; and *erm*(B), 8–32 mg/L for both. In contrast, 24 (87.5%) of 28 erythromycin-resistant isolates had a telithromycin MIC ≤1.0 mg/L (range 0.015–8 mg/L), including all isolates with the *erm*(TR) (inducible MLS resistance) and *mef*(A)

Table 3. Satisfactory bacteriological outcome at the post-therapy/test of cure and late post-therapy visits in patients treated with telithromycin (800 mg once-daily) for 5 days or a comparator antibacterial agent[a] for 10 days in patients with GABHS tonsillopharyngitis

	No. of patients (%) PP			No. of patients (%) bmITT		
	Telithromycin	Comparator[a]	95% CI	Telithromycin	Comparator[a]	95% CI
Post-therapy, test of cure (days 16–23)						
Study 3004	97/115 (84.3)	106/119 (89.1)	− 14.3; 4.8	110/138 (79.7)	119/150 (79.3)	− 9.6; 10.4
Study 3008	137/150 (91.3)	119/135 (88.1)	− 4.6; 11.0	152/187 (81.3)	134/173 (77.5)	− 5.0; 12.8
Combined	234/265 (88.3)	225/254 (88.6)	− 6.2; 5.6	262/325 (80.6)	253/323 (78.3)	− 4.2; 8.8
Late post-therapy (days 31–45)						
Study 3004	89/108 (82.4)	94/111 (84.7)	13.0; 8.5	103/138 (74.6)	109/150 (72.7)	− 8.9; 12.8
Study 3008	112/136 (82.4)	98/120 (81.7)	− 9.5; 10.9	133/187 (71.1)	116/173 (67.1)	− 6.0; 14.2
Combined	201/244 (82.4)	192/231 (83.1)	− 8.0; 6.5	236/325 (72.6)	225/323 (69.7)	− 4.3; 10.2

[a]Penicillin V 500 mg three-times-daily or clarithromycin 250 mg twice-daily.
BmITT, bacteriological modified intent-to-treat; CI, confidence interval; PP, per protocol.

(resistance by efflux) genes. Four isolates with a telithromycin MIC of 8.0 mg/L had the *erm*(B) (constitutive MLS resistance) genotype. However, the remaining *erm*(B) isolate, and all isolates harbouring *erm*(B) in combination with *mef*(A) (3/3), had a telithromycin MIC ≤1.0 mg/L.

Bacteriological outcome

In Study 3004, a satisfactory bacteriological outcome was demonstrated for 84.3% of patients treated with telithromycin and 89.1% of patients treated with penicillin V at the post-therapy/TOC visit in the PP population (Table 3). In the bmITT population, response rates were 79.7% in the telithromycin group, and 79.3% in the penicillin V group. In Study 3008, 91.3% of telithromycin-treated patients and 88.1% of clarithromycin-treated patients in the PP population had satisfactory bacteriological outcomes at the post-therapy/TOC visit (respective rates for the bmITT population were 81.3% and 77.5%) (Table 3). Equivalence was demonstrated between therapy with telithromycin for 5 days and the individual comparators for 10 days (Table 3). Similar results were observed in both the PP and bmITT populations, and equivalence between treatments was demonstrated at the LPT visit (Table 3).

In Study 3004, *S. pyogenes* was eradicated in 85.2% (98/115) of telithromycin-treated patients and 89.1% (106/119) of penicillin V-treated patients at the post-therapy/TOC visit (Fig. 2). Eradication rates were 86.1% (93/108) and 86.5% (96/111) for telithromycin- and penicillin V-treated patients, respectively, at the LPT visit. In Study 3008, eradication rates were 91.3% (137/150) in the telithromycin-treated patients and 88.9% (120/135) in the clarithromycin-treated patients at the post-therapy/TOC visit, and 84.6% (115/136) and 82.5% (99/120), respectively, at the LPT visit (Fig. 2).

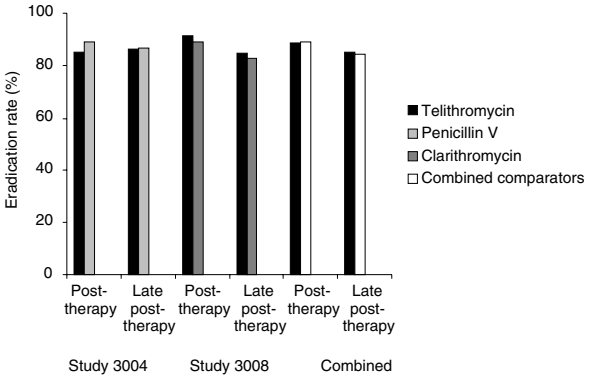

Fig. 2. Bacteriological eradication rates for *Streptococcus pyogenes* at the post-therapy/test of cure and late post-therapy visits in patients treated with telithromycin (800 mg once-daily) for 5 days or a comparator antibacterial agent (penicillin V 500 mg three-times-daily or clarithromycin 250 mg twice-daily) for 10 days (per-protocol population).

Combining the data from both studies revealed that 88.3% of patients treated with telithromycin had a satisfactory bacteriological outcome compared with 88.6% of comparator-treated patients at the post-therapy/TOC visit (Table 3). An overall GABHS eradication rate of 88.7% (235/265) was obtained for telithromycin and of 89.0% (226/254) for pooled comparators at the post-therapy/TOC visit. Similar results were observed at the LPT visit (Table 3; Fig. 2).

An analysis of the influence of various clinical and demographic factors on bacteriological outcome at the post-therapy/TOC visit demonstrated that GABHS infection in the last 12 months, previous ear-, nose- or throat-related surgery, gender, age and smoking status had no significant effect on outcome in the telithromycin or comparator groups. Overall, the presence of cervical lymphadenopathy or exudate did not influence

Table 4. Clinical cure rates at the post-therapy/test of cure and late post-therapy visits in patients treated with telithromycin (800 mg once-daily) for 5 days or a comparator antibacterial[a] for 10 days in patients with GABHS

	No. of patients (%) PP			No. of patients (%) mITT		
	Telithromycin	Comparator[a]	95% CI	Telithromycin	Comparator[a]	95% CI
Post-therapy, test of cure (days 16–23)						
Study 3004	109/115 (94.8)	112/119 (94.1)	− 6.1; 7.4	170/198 (85.9)	169/197 (85.8)	− 7.3; 7.5
Study 3008	139/150 (92.7)	123/135 (91.1)	− 5.5; 8.6	193/232 (83.2)	192/231 (83.1)	− 7.2; 7.3
Combined	248/265 (93.63)	235/254 (92.5)	− 3.7; 5.8	363/430 (84.4)	361/428 (84.3)	− 5.0; 5.2
Late post-therapy (days 31–45)						
Study 3004	100/108 (92.6)	100/111 (90.1)	− 5.8; 10.9	161/198 (81.3)	163/197 (82.7)	− 9.5; 6.6
Study 3008	120/134 (89.6)	103/118 (87.3)	− 96.5; 11.0	178/232 (76.7)	170/231 (73.6)	− 5.2; 11.4
Combined	220/242 (90.94)	203/229 (88.6)	− 3.6; 8.2	339/430 (78.8)	333/428 (77.8)	− 4.7; 6.8

[a]Penicillin V 500 mg three-times-daily or clarithromycin 250 mg twice-daily.
mITT, modified intent-to-treat; CI, confidence interval; PP, per protocol.

significantly the bacteriological outcome in the treatment groups, with eradication rates in these subgroups being comparable to those in the total PP population.

Clinical outcome

Clinical cure rates in patients treated with telithromycin were equivalent to those observed with penicillin V and clarithromycin at both post-therapy and late post-therapy visits (Table 4). At the post-therapy/TOC visit, clinical cure rates in telithromycin-treated patients were 92.7–94.8% (mean 93.6%), compared with 94.1% in penicillin V-treated patients and 91.1% in clarithromycin-treated patients (per-protocol). In Study 3004 at LPT, clinical cure rates were 92.6% and 90.1% for telithromycin- and penicillin V-treated patients, respectively. Corresponding values in Study 3008 were 89.6% for patients treated with telithromycin and 87.3% for those treated with clarithromycin (Table 4). In each study, the clinical efficacy results obtained in the mITT population confirmed the results obtained in the PP population.

Efficacy in patients with erythromycin-resistant strains of GABHS

Eleven erythromycin-resistant strains of *S. pyogenes* (MIC ≥ 1.0 mg/L) were isolated from telithromycin-treated patients in the PP population. Bacterial eradication of erythromycin-resistant strains was achieved in three patients at the post-therapy/TOC visit and in six patients at the LPT visit. Interestingly, clinical cure was attained in ten of these patients at the post-therapy/TOC visit and in nine patients at the LPT visit.

Four erythromycin-resistant strains of *S. pyogenes* were isolated from clarithromycin-treated patients. Bacterial eradication of erythromycin-resistant strains was achieved from four patients at both the post-therapy/TOC and LPT visits, while clinical cure was attained in two of these patients at the post-therapy/TOC and LPT visits. In total, nine erythromycin-resistant strains of *S. pyogenes* were isolated from penicillin-treated patients. Bacterial eradication and clinical cure was achieved with eight of these strains at both the post-therapy/TOC and LPT visits.

Safety

Safety data were available for 851 of the 858 patients in the mITT population. In Study 3004, treatment-emergent adverse events (TEAEs) were reported by 35.4% (70/198) of patients treated with telithromycin and 35.2% (69/196) of patients treated with penicillin V. In Study 3008, these values were 67.2% (154/229) and 57.5% (60/228) for telithromycin- and clarithromycin-treated patients, respectively.

Most of the adverse events were mild or moderate in intensity for all treatment groups. Diarrhoea was the most common treatment-related adverse event in the telithromycin- and comparator-treated patients, but caused < 1% of patients in both groups to discontinue treatment. Gastrointestinal adverse events (diarrhoea, nausea, vomiting or gastrointestinal pain) that were considered by the investigator to be possibly related to treatment (and occurred in ≥ 2% of patients) affected 22.7% (45/198) and 32.3% (74/229) of telithromycin-treated patients in Studies 3004 and 3008, respectively. In contrast, 5.6% (11/196) and 11.4% (26/228) of penicillin V- and clarithromycin-treated patients, respectively, experienced gastrointestinal adverse events. The majority of gastrointestinal events were of mild intensity for telithromycin-treated patients (72/119; 60.5%) and comparator-treated patients

(27/37; 73.0%). Discontinuations as a result of all treatment-related adverse events were few and similar in telithromycin- and comparator-treated patients, ranging between 4.5% and 5.7%, and 3.9% and 4.1%, respectively. There were no relevant differences between the treatment groups in terms of clinically noteworthy abnormal laboratory values. No clinically noteworthy ECG QTc changes (QTc > 500 ms) were observed in telithromycin- or clarithromycin-treated patients in Study 3008.

DISCUSSION

This analysis pools data from the first two studies to report on the efficacy and safety of telithromycin in the treatment of GABHS tonsillopharyngitis in adolescent and adult patients. The results reveal that a course of telithromycin 800 mg once-daily for 5 days is as effective as treatment with penicillin V (500 mg three-times-daily) or clarithromycin (250 mg twice-daily) for 10 days in terms of bacteriological and clinical outcome.

Penicillin V is the current treatment of choice for GABHS tonsillopharyngitis on the basis of its efficacy, tolerability and low cost [29]. However, bacteriological and clinical failure rates with penicillin therapy have been increasing steadily since the late 1970s and are now in the region of 30% in some studies [12]. Lack of adherence to the 10-day therapeutic regimen is thought to be the primary cause of penicillin treatment failure in cases of GABHS tonsillopharyngitis [12]. Alternative therapies include the macrolides, such as clarithromycin, which are preferable for those patients who are allergic to penicillin [4,5]. However, the recent rapid increase in macrolide resistance rates among *S. pyogenes* isolates [6–10] threatens the usefulness of this group of drugs in the treatment of patients with GABHS tonsillopharyngitis who are allergic to penicillin. The limitations of current treatment options have led to the search for effective agents whose antibacterial activity extends to macrolide-resistant strains of *S. pyogenes*.

Telithromycin has a targeted spectrum of activity against key respiratory pathogens, including *S. pyogenes*. In-vitro studies have revealed that telithromycin has potent antibacterial activity against *S. pyogenes*, including macrolide-resistant strains [17–19], and results from these studies confirmed that the in-vitro coverage provided by telithromycin against clinical isolates of *S. pyogenes* was superior to that observed with either clarithromycin or azithromycin.

Macrolide resistance in *S. pyogenes* is mediated principally by the products of two genes: methylases encoded by the *erm* genes result in modification of the 23S ribosomal RNA drug-binding site, while the *mef* gene codes for an efflux pump, resulting in an active efflux of macrolide from the cell. Target-site modification can be expressed in either a constitutive or inducible manner, and confers co-resistance to all MLS_B antimicrobials [30]. The macrolide efflux system (M phenotype) confers resistance to other 14- and 15-membered macrolides, but not to the rest of the MLS group [31]. The prevalence of these two resistance mechanisms varies geographically. Recent results from an international surveillance study [32] indicated that whereas the *erm*(TR) genotype predominated in the USA and Canada, *mef*(A) was the most common genotype among *S. pyogenes* isolates worldwide. This contrasted with the distribution of genotypes observed among *S. pneumoniae* isolates, where in the USA most macrolide-resistant strains were *mef*(A) positive, while worldwide the *erm*(B) genotype predominated. In these studies, the in-vitro coverage against clinical isolates of *S. pyogenes* provided by telithromycin also extended to isolates resistant to erythromycin. Telithromycin MICs varied, depending on the mechanism of erythromycin resistance: *erm*(TR), 0.015–0.06 mg/L; *mef*(A), 0.5–1.0 mg/L; and *erm*(B), 0.5–8.0 mg/L. In contrast, MICs were higher for clarithromycin and azithromycin according to genotype: *erm*(TR), 1–4 mg/L and 16–32 mg/L, respectively; *mef*(A), 4–16 mg/L and 8–16 mg/L, respectively; *erm*(B), 8–32 mg/L for both.

Combining the data from the present two studies revealed that a satisfactory bacteriological outcome was achieved in 88.3% of patients treated with telithromycin and 88.6% of patients treated with penicillin V or clarithromycin at the post-therapy/TOC visit. The eradication rates for *S. pyogenes* were similar in all three treatment groups. The overall clinical cure rates were 93.6% and 92.5% in telithromycin- and pooled comparator-treated patients, respectively, at the post-therapy/TOC visit. Statistical analysis confirmed that telithromycin and comparator antibacterial treatment were equivalent in terms of bacteriological and clinical outcome. An important consideration is the stringent nature of this study

design, with TOC assessed 16–23 days after initiation of treatment (i.e., 11–18 days after completion of telithromycin and 6–10 days after completion of comparator antibacterials). Unlike studies in which outcome is assessed at the end of therapy, this approach includes early cases of relapse and thus represents a more rigorous evaluation of efficacy.

Among the 11 patients who received telithromycin and had erythromycin-resistant GABHS isolates, most (90.9%) achieved clinical cure compared with 76.9% patients in the comparator-treated group. Despite good clinical efficacy, eradication of the erythromycin-resistant isolates was lower in the telithromycin-treated group than in the penicillin V-treated group. However, eradication of these isolates was greater than with clarithromycin, particularly at the late post-therapy visit, although the numbers were too small to allow definite conclusions to be drawn. Despite the low numbers, the increased clinical and bacteriological efficacy of telithromycin compared with clarithromycin, combined with its retained in-vitro activity against resistant *mef*(A)- and *erm*(TR)-positive strains vs. clarithromycin and azithromycin, suggests that telithromycin may be a useful treatment option in geographical regions where these genotypes predominate and when β-lactams cannot be used.

Although the reasons for recurrence of GABHS tonsillopharyngitis are multifactorial, non-adherence plays an important role [13,29]. Often, 2–3 days after the initiation of antibacterial therapy, patients will experience an improvement in their symptoms and some forego the remaining medicine. Poor adherence to antibacterial regimens of 7–10 days contributes significantly to treatment failure in acute respiratory tract infections [33]. Therefore, shorter treatment durations may be associated with improved treatment adherence. However, in order to achieve practical pharyngeal eradication of GABHS, most oral antibacterial agents must be administered for 10 days [1,34]. Attempts to reduce the duration of treatment with penicillin V have led to increased rates of bacteriological failure [34,35]. In a recent study comparing different durations of treatment of macrolide therapy in the eradication of group A streptococci from the throat, a 10-day course of clarithromycin was more effective than treatment with azithromycin for 5 days [36]. In the present studies, patient adherence to all treatments was good, with no difference between the telithromycin and comparator groups in terms of those patients taking at least 70% of their medication. Of note in both studies was the fact that full adherence over the first 5 days of treatment was higher than for the total 10-day duration of therapy for all three treatments. The more convenient once-daily dosing schedule and short treatment courses could lead to better adherence to telithromycin regimens in the outpatient setting, thereby minimising the risk of treatment failure.

Telithromycin was generally well-tolerated in both studies, with most adverse events being of mild or moderate intensity. Gastrointestinal adverse events were more common in telithromycin-treated patients; however, they were not treatment limiting. Furthermore, the number of discontinuations caused by adverse events was similar in patients treated with telithromycin and comparators.

In conclusion, the ability of short-course (5-day) treatment with telithromycin to achieve clinical cure and bacteriological eradication rates comparable to those obtained with treatment with standard comparator antibacterial agents for 10 days, with in-vitro activity improved over that of clarithromycin and azithromycin, together with the convenience of once-daily dosing, makes telithromycin an attractive alternative to β-lactams for the treatment of GABHS tonsillopharyngitis in adolescents and adults. Improved adherence over the first 5 days of treatment further supports the use of an agent with a shorter duration of treatment.

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