

## Flurbiprofen microgranules for relief of sore throat:

a randomised, double-blind trial

### Abstract

#### Background

Many people with sore throat seek, and are often inappropriately prescribed, antibiotics.

#### Aim

The objective of this study was to determine the analgesic efficacy of flurbiprofen 8.75 mg microgranules versus placebo. These microgranules are a possible alternative treatment for patients with sore throat due to upper respiratory tract infection (URTI).

#### Design and setting

Randomised, double-blind, placebo-controlled, multiple-dose study conducted at eight primary care sites in Australia.

#### Method

Participants with sore throat of onset within the past 4 days received either flurbiprofen 8.75 mg microgranules or non-medicated placebo microgranules. Throat soreness, difficulty in swallowing, sore throat pain intensity, sore throat relief, oral temperature, and treatment benefits were all assessed at regular intervals.

#### Results

Of 373 patients from eight centres, 186 received flurbiprofen 8.75 mg microgranules and 187 received placebo microgranules (intent-to-treat population). Throat soreness was significantly reduced over the first 2 hours after the first dose. Reductions in difficulty in swallowing were observed at all time points from 5 to 360 minutes after the first dose, after taking flurbiprofen microgranules versus placebo. Sore throat relief was also evident at 1 minute and lasted for at least 6 hours. The multiple-dose efficacy results showed reduction of difficulty in swallowing at the end of days 1–3 and sore throat relief at the end of day 1.

#### Conclusion

Microgranules containing flurbiprofen 8.75 mg provided fast and effective relief from sore throat due to URTI and represent an alternative treatment option to antibiotic therapy.

#### Keywords

Analgesic; anti-inflammatory agent; primary health care; sore throat; swallowing.

### INTRODUCTION

Viruses are the cause of ~80% of sore throats associated with upper respiratory tract infections (URTIs).<sup>1</sup> However, many people with sore throat seek, and are often inappropriately prescribed, antibiotics.<sup>2–4</sup> Misuse of antibiotics promotes the development of antibiotic-resistant bacterial strains,<sup>5,6</sup> which are unresponsive to treatment. Thus antibiotics should only be recommended for sore throat when the presence of a bacterial infection is confirmed or likely. In the UK, the National Institute for Health and Clinical Excellence (NICE) advises a strategy of no or delayed antibiotic prescribing for acute sore throat, unless clinical signs and symptoms indicate a serious illness.<sup>7</sup>

A lack of alternative products to recommend or prescribe may explain the widespread use of antibiotics for treatment of sore throat. Studies support the single- and multi-dose efficacy of flurbiprofen 8.75 mg lozenges for the symptomatic treatment of sore throat.<sup>8–11</sup> These lozenges are available as an over-the-counter medicine in several countries, including the UK (marketed as Strefen® [Reckitt Benckiser]), Italy, New Zealand, and Australia. In this study, the efficacy of flurbiprofen 8.75 mg microgranules (registered as Strefen Instants 8.75 mg granules in the UK) was assessed in patients with sore throat due to URTI. They are a novel delivery format

and their bioequivalence to the lozenges has been demonstrated (Reckitt Benckiser, unpublished data, 2009). Flurbiprofen microgranules dissolve directly on the tongue without water and form a liquid, which is swallowed. They are ideal for use at night when sucking a lozenge is inconvenient, and are intended to provide rapid relief of pain from sore throat.

This study's primary objective was to determine the analgesic properties of flurbiprofen 8.75 mg microgranules up to 2 hours after the first dose in patients with sore throat due to URTI. Throat soreness, difficulty in swallowing, sore throat pain intensity, sore throat relief, and oral temperature were evaluated. Patient/consumer treatment benefits were also assessed.

### METHOD

This was a randomised, double-blind, parallel-group, placebo-controlled, multiple-dose study at eight primary care sites in Australia.

#### Patient selection

Between June and September 2009, participants with sore throat due to URTI were recruited after presenting opportunistically to their GP, or after responding to advertisements in local medical practice surgeries.

The inclusion criteria were: aged

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### How this fits in

The misuse of antibiotics by the medical professional is common and many patients are wrongly prescribed antibiotics for sore throat. In this study, microgranules containing flurbiprofen 8.75 mg, a novel analgesic format, were assessed in patients suffering from sore throat and found to be very effective in relieving pain and associated symptoms. This over-the-counter treatment is a potential alternative to antibiotic therapy.

18–75 years; sore throat due to URTI with onset  $\leq 4$  days; score of  $\geq 6$  on a throat soreness 11-point ordinal scale; score of  $\geq 5$  on the expanded 21-point Tonsillopharyngitis Assessment scale.

The exclusion criteria were: history of allergy; intolerance/sensitivity to any of the study medications; evidence of mouth breathing or severe coughing; any condition in the previous  $\leq 8$  weeks that could compromise breathing; any painful condition that may distract from sore throat pain; history of severe renal or hepatic impairment; glutathione depletion; painful comorbidities requiring analgesics; stomach and peptic ulcers; smokers unable to refrain from smoking in the clinic; overt alcohol abuse; women who were pregnant, lactating, or not using adequate contraception; those who had participated in a clinical trial in the previous  $\leq 30$  days; and patients who had taken one of the following: demulcents or throat sprays  $\leq 2$  hours previously, sore throat medication with local anaesthetic  $\leq 4$  hours previously, analgesic, antipyretic or cold medication  $\leq 8$  hours previously, longer-acting or slow-release analgesics  $\leq 24$  hours previously, antibiotics or drugs that induce liver enzymes  $\leq 14$  days previously, and those currently taking warfarin or other coumarins.

### Randomisation and treatment

Patients were randomised in blocks of four, according to a numbered computer-generated sequence, to receive sachets containing either flurbiprofen 8.75 mg microgranules or matching placebo. Both patients and investigators were blinded to treatment. Patients were advised to tilt their head back and tip the entire contents of the sachet towards the back of the mouth and swallow.

Participants were assessed in clinic for 3 hours and then discharged. They were

given trial medication, rescue medication (two tablets of 500 mg paracetamol [Panadol Advance®, GSK, UK]), and a patient diary to record their medication consumption. Patients were instructed not to take additional trial or rescue medication within 6 hours after the first dose. After 6 hours, they could take one sachet of trial medication every 3–6 hours ( $\leq 5$  doses/day, for up to 3 days) or rescue medication ( $\leq 4$  doses/day), as required. If the patient's sore throat resolved before day 3, trial medication was discontinued. Patients returned to the clinic for a final visit 1–4 days after the day 3 assessments, with their completed diaries and unused trial and rescue medication.

### Outcome measures

The outcome measures were throat soreness (11-point ordinal scale; 0 = not sore and 10 = very sore),<sup>9</sup> difficulty in swallowing (100 mm visual analogue scale [VAS]),<sup>12</sup> sore throat pain intensity (100 mm VAS),<sup>11</sup> and sore throat relief (7-point sore throat relief scale, 0 = no relief to 6 = complete relief).<sup>9</sup> These were assessed at 1 minute before the first dose (with exception of sore throat relief), at 1 minute after the first dose, at 5-minute intervals up to 15 minutes, then at 15-minute intervals up to 180 minutes and hourly up to 360 minutes after the first dose.

Additionally, difficulty in swallowing and sore throat relief were assessed at the end of day 1, at 24 hours after the first dose, and at the end of days 2 and 3. Oral temperature was taken at 60, 120, and 180 minutes after the first dose. Participants completed a consumer questionnaire at the end of day 3, by answering the following: 'Do you feel less frustrated than before you took the microgranules?', 'Do you feel less distracted than before you took the microgranules?', and 'Do you feel happier than before you took the microgranules?'.

### Study endpoints

The primary efficacy endpoint was the area under the curve (AUC) for change in severity of throat soreness, from baseline to 2 hours after the first dose.

Secondary endpoints included the AUC from baseline to 3 and 6 hours after the first dose for changes in throat soreness, difficulty in swallowing, sore throat pain intensity, and sore throat relief. Changes from baseline in difficulty in swallowing and sore throat relief were also assessed at the end of day 1, at 24 hours after the first dose, and at the end of days 2 and 3.

The methodology was based on the

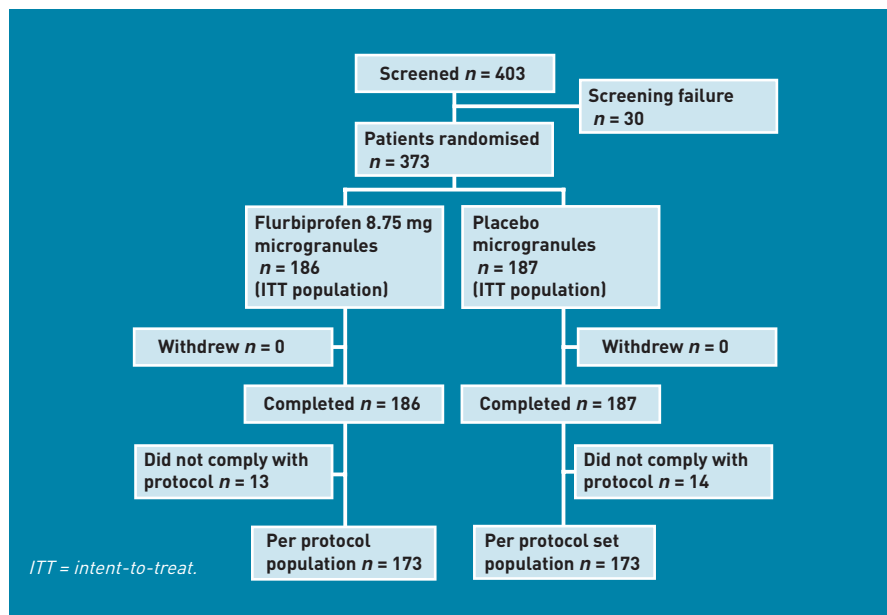


Figure 1. Patient study flow chart.

accepted and validated Sore Throat Pain Model methodology,<sup>13–20</sup> which has also been employed in previous studies of flurbiprofen-containing sore-throat lozenges.<sup>8–10</sup>

#### Statistical analysis

All raw data were listed and sorted by patient randomisation number (including patient initials) and visit/assessment (that is, time point), where applicable.

An overall difference of 0.34 in AUC in throat soreness severity between flurbiprofen and placebo lozenges has been observed.<sup>8–10</sup> Therefore, to detect a difference of 0.4 (two-sided t-test at 5% significance level), 185 patients per group were required to provide 90% power. A difference of 0.4 was chosen because microgranules were believed to offer lower demulgency potential and a lower-magnitude placebo effect compared with lozenges.

Continuous data were summarised using descriptive statistics. All statistical

tests performed were two-sided at a 5% significance level, unless otherwise stated. The statistical package used was SAS (version 9.1.3).

The primary and secondary endpoints were analysed using analysis of covariance (ANCOVA) with baseline values as covariates and factors for treatment group and centre using data from all randomised patients who took at least one dose of study medication (intent-to-treat population). Analyses were also performed on data from those patients who satisfied the inclusion/exclusion criteria, who correctly received their randomised treatment, and who successfully completed the treatment up to the 2-hour primary efficacy endpoint (per protocol population). The statistical analysis was not adjusted for multiple comparisons.

For the consumer questionnaire, binary response questions were analysed using a logistic regression model with factors for treatment group and centre, and a covariate for baseline throat soreness severity.

#### Safety

The incidence of adverse events reported spontaneously by the patient, or in response to questioning or observation by the investigator, was assessed. Any relationship to the study medication was determined by the investigator or by a medically qualified co-investigator.

#### RESULTS

##### Patient population

Of 403 patients initially screened, 373 patients from eight centres were randomised to receive flurbiprofen 8.75 mg ( $n = 186$ ) or placebo ( $n = 187$ ) microgranules (intent-to-treat population; Figure 1). Treatment groups were generally well balanced (Table 1). Twenty-seven patients were then excluded from the intent-to-treat population, to form the per protocol population ( $n = 346$ ). The protocol deviations included non-completion

Table 1. Baseline patient demographics and characteristics; intent-to-treat population

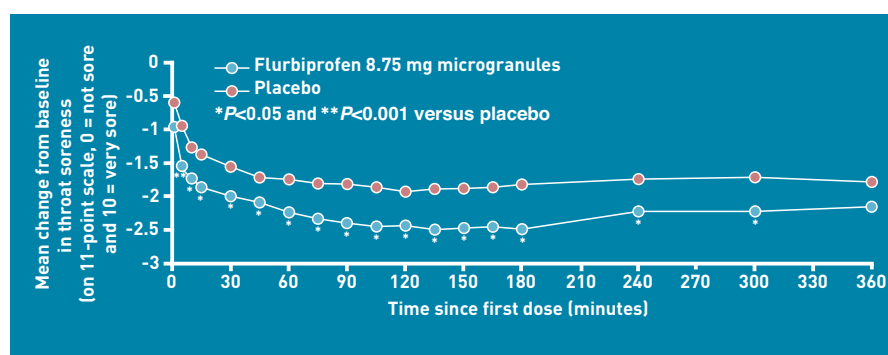
	Flurbiprofen 8.75 mg	Placebo
Number of patients	186	187
Age, years	30.8 ± 13.4	30.4 ± 13.6
TPA score <sup>a</sup>	7.59 ± 2.18	7.51 ± 2.08
Throat soreness <sup>b</sup>	6.78 ± 0.78	6.73 ± 0.87
Difficulty in swallowing <sup>c</sup>	63.1 ± 14.8	62.1 ± 14.9
Sore throat pain intensity <sup>c</sup>	61.4 ± 12.3	61.8 ± 13.0

Data are mean ± standard deviation. TPA = Tonsillopharyngitis Assessment. <sup>a</sup>21-point ordinal scale. <sup>b</sup>11-point ordinal scale. <sup>c</sup>100 mm visual analogue scale.

**Table 2. Area under the change from baseline curve from 0 to 2 hours for throat soreness (measured on an 11-point scale where 0 = not sore and 10 = very sore)**

	Flurbiprofen 8.75 mg	Placebo
<b>Intent-to-treat population</b>		
<i>n</i>	186	187
Mean ± SD	-2.14 ± 1.735	-1.65 ± 1.668
Least squares mean <sup>a</sup>	-2.29	-1.81
Difference between least squares means <sup>b</sup>	-0.48	
95% CI	-0.81 to -0.15	
<i>P</i> -value for treatment <sup>a</sup>	0.0049	
<b>Per protocol population</b>		
<i>n</i>	173	173
Mean ± SD	-2.14 ± 1.770	-1.67 ± 1.670
Least squares mean <sup>a</sup>	-2.29	-1.83
Difference between least squares means <sup>b</sup>	-0.46	
95% CI	-0.81 to -0.11	
<i>P</i> -value for treatment <sup>a</sup>	0.0097	

<sup>a</sup>Estimated from analysis of covariance model with factors for treatment and centre and a covariate for baseline throat soreness severity. <sup>b</sup>Flurbiprofen 8.75 mg microgranules minus placebo. A negative difference favours flurbiprofen 8.75 mg microgranules. SD = standard deviation.



**Figure 2. Intent-to-treat population: mean change from baseline in throat soreness from 1 to 360 minutes post-first dose.**

of the 2-hour primary efficacy endpoint treatment ( $n = 15$ ); inadmissible start time of follow-up assessments ( $n = 9$ ); inadmissible concomitant medication ( $n = 2$ ); and violation of inclusion/exclusion criteria ( $n = 1$ ).

The percentage of patients taking rescue medication was similar between groups, as was the overall number of sachets taken. Only 5.4% and 5.9% of patients taking the flurbiprofen 8.75 mg and placebo microgranules, respectively, took rescue medication in the first 6 hours post-dose. The mean number of sachets taken was 5.18 and 5.24 for the flurbiprofen 8.75 mg and placebo groups, respectively.

#### Primary efficacy endpoint

In the intent-to-treat population, the difference between the least squares (LS) mean for the AUC in severity of throat soreness from baseline to 2 hours was statistically significant for the flurbiprofen 8.75 mg microgranules group over the first

2 hours [ $-0.48$ ; 95% confidence interval (CI) =  $-0.81$  to  $-0.15$ ,  $P = 0.0049$ ]. The results were quantitatively consistent in the per protocol population (Table 2).

#### Secondary efficacy endpoints

**Single-dose efficacy results.** Overall, flurbiprofen 8.75 mg microgranules showed superiority to placebo in reducing both pain and difficulty in swallowing. The effect of all assessed parameters peaked at 90–180 minutes post-dose.

The mean change from baseline in throat soreness was significantly greater in patients taking flurbiprofen microgranules versus placebo at all time points up to 300 minutes post dose ( $P < 0.05$ ) (Figure 2). The difference in AUC from baseline to 3 and 6 hours for throat soreness was significant with flurbiprofen microgranules versus placebo ( $P = 0.0035$  and  $P = 0.0051$ , respectively). Significant decreases in difficulty in swallowing were also observed with flurbiprofen microgranules versus placebo from 5 to 360 minutes after the first dose ( $P < 0.05$ ), and at 3 and 6 hours in the AUC analysis ( $P = 0.0011$  and  $P = 0.0003$ , respectively). The mean change in sore throat pain intensity was significantly greater for flurbiprofen microgranules compared with placebo at all time points ( $P < 0.05$ ), apart from 1, 15, 30, and 45 minutes post-dose. The AUC was significantly higher with flurbiprofen microgranules versus placebo at 3 and 6 hours ( $P = 0.0048$  and  $P = 0.0021$ , respectively). Furthermore, the mean sore throat relief was significantly greater with flurbiprofen microgranules versus placebo from 1 minute ( $P = 0.0006$ ) up to 360 minutes ( $P < 0.05$ ). The AUC analyses also showed a significant difference at 3 and 6 hours ( $P = 0.0020$  and  $P = 0.0043$ , respectively).

Changes from baseline in oral temperature ( $^{\circ}\text{C}$ ) were significantly different between groups at 180 minutes post-dose ( $-0.3$  for flurbiprofen versus  $-0.1$  for placebo,  $P = 0.015$ ).

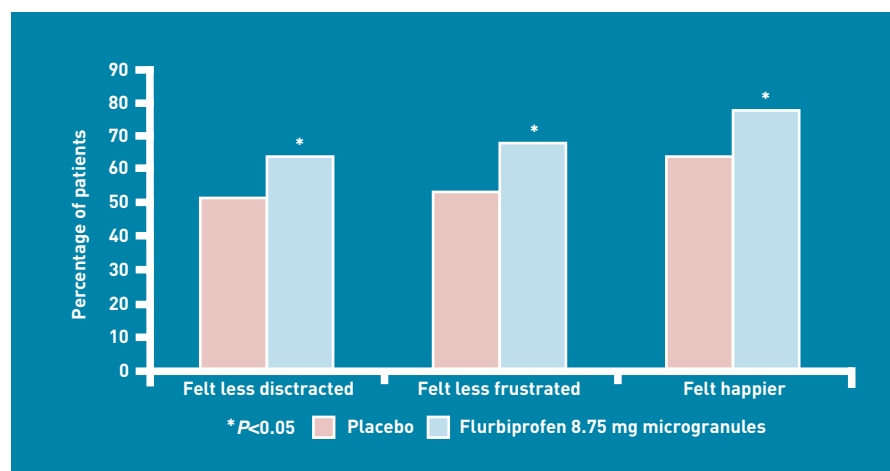
**Multiple-dose efficacy results.** At the end of days 1, 2, and 3, there was a significantly greater mean change from baseline in difficulty in swallowing with flurbiprofen microgranules compared with placebo ( $P = 0.018$ ,  $P = 0.016$ , and  $P = 0.032$ , respectively).

The difference in least squares means in sore throat relief favoured the flurbiprofen 8.75 mg microgranules group at the end of day 1, 24 hours after the first dose, and at the end of days 2 and 3. However, significance was only achieved at the end of day 1 ( $P = 0.026$ ) (Table 3).

**Table 3. Change from baseline in difficulty in swallowing<sup>a</sup> and sore throat relief<sup>b</sup> at the end of day 1, at 24 hours post-first dose, and at the end of days 2 and 3; intent-to-treat population**

	Difficulty in swallowing			Sore throat relief		
	Difference between least squares means <sup>c</sup>	95% CI	P-value for treatment	Difference between least squares means <sup>a</sup>	95% CI	P-value for treatment
End of day 1	-5.55	-10.15 to -0.94	0.018	0.42	0.05 to 0.80	0.026
24 hours post-first dose	-4.31	-8.79 to 0.16	0.059	0.28	-0.10 to 0.66	0.150
End of day 2	-5.74	-10.39 to -1.09	0.016	0.33	-0.06 to 0.73	0.101
End of day 3	-5.12	-9.80 to -0.43	0.032	0.38	-0.04 to 0.79	0.078

<sup>a</sup>Measured on 100 mm visual analogue scale where 0 mm = no difficulty, 100 mm = very difficult. <sup>b</sup>Measured on a 7-point scale where 0 = no relief, 6 = complete relief. <sup>c</sup>Flurbiprofen 8.75 mg microgranules minus placebo.



**Figure 3. Percentage of patients who felt less distracted, less frustrated, and happier after taking their pre-assigned microgranules at the end of day 3.**

**Consumer questionnaire.** At the end of day 3, patients felt significantly less distracted, less frustrated, and happier after taking the flurbiprofen microgranules compared with placebo ( $P < 0.05$ ) (Figure 3).

### Safety

The proportion of patients reporting treatment-emergent adverse events was similar between treatment groups (23.1% for flurbiprofen versus 29.4% for placebo). The majority of adverse events were mild and most of those were related to the patient's URTI (for example, headache, cough, chills, and pyrexia). The incidence of gastrointestinal adverse events was low and similar between treatment groups (4.8% for flurbiprofen versus 4.3% for placebo). The most common adverse event was headache, with 26 (14.0%) patients reporting 35 headaches in the flurbiprofen group and 37 (19.8%) patients reporting 53 headaches in the placebo group. No

serious adverse events were reported.

## DISCUSSION

### Summary

Novel flurbiprofen 8.75 mg microgranules were effective in providing relief from sore throat due to URTIs. Their superiority over placebo was clearly apparent, with statistically significant differences for the majority of the analgesic variables related to throat soreness: difficulty in swallowing, sore throat pain intensity, and sore throat relief. The multiple-dose efficacy results showed sore throat relief at the end of day 1 but not at the subsequent time points assessed over 1–3 days. This may be explained by the relatively low numbers of repeat dose sachets taken and the gradual recovery of patients from their sore throat. However, patients rated the microgranules significantly better as an overall treatment, compared with placebo.

### Strengths and limitations

This was the first randomised, controlled study to investigate the efficacy of flurbiprofen microgranules for treatment of sore throat. The results were robust, and similar conclusions were obtained for both the intent-to-treat and per protocol analysis populations, where performed.

No safety issues were reported. Despite the high prevalence of gastrointestinal adverse events associated with oral non-steroidal anti-inflammatory drug (NSAID) therapy,<sup>21</sup> the short-term intake of flurbiprofen microgranules did not increase the incidence of gastrointestinal-related adverse events in this predominantly young population.

One possible limitation to this study is the use of subjective measures. Throughout the study, the ANCOVA covariates of centre, throat soreness, and difficulty in swallowing were generally statistically significant when analysing the endpoints of throat soreness and difficulty in swallowing. This suggests, as expected from a subjective painful condition, that patients from different centres with different baseline characteristics assessed their response to treatment to different degrees. Moreover, the results from the consumer questionnaire need to be interpreted with caution, owing to the broad nature of the questions.

Another possible limitation is the fact that the statistical analysis was not adjusted for multiple comparisons. Therefore, the results from any secondary endpoint are purely supportive of the primary endpoint and are not confirmatory.

### Comparison with existing literature

For the primary endpoint, the difference between the least squares means of  $-0.48$  was greater than the overall difference of  $-0.34$  observed in previous studies with flurbiprofen 8.75 mg lozenges.<sup>8-10</sup> The maximum reductions in throat soreness were seen 90–180 minutes post-dose.

Pain relief was evident by 1 minute post-dose and lasted for at least 6 hours. Previous reports have shown that a reduction of 1–2 points on an 11-point ordinal scale represents a clinically important difference.<sup>22-24</sup> A change in this score of  $-2.0$  was best associated with the concept of 'much better' improvement.<sup>22</sup> Therefore, the degree of change in throat soreness achieved with flurbiprofen microgranules was clinically relevant from 30 minutes post-dose and up to 6 hours.

Although there was a statistically significant reduction in oral temperature at 3 hours post-dose, the potential clinical relevance of this is unclear. Previous studies using flurbiprofen lozenges that also measured oral temperature have not reported any changes.<sup>8-10</sup>

### Implications for research and practice

The flurbiprofen 8.75 mg microgranules are an effective, fast-acting and well-tolerated over-the-counter treatment option for patients with sore throat associated with URIs, and provide GPs with an alternative treatment to antibiotic therapy. In the UK, GPs following NICE's strategy of no or delayed antibiotic prescribing should consider recommending suitable over-the-counter treatments for patients presenting with sore throat.

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We are grateful to Reckitt Benckiser Healthcare International Ltd for funding this study.

### Ethical approval

Ethical approval was given by Bellbery Ethics Committee, Adelaide, Australia. The study was conducted in accordance with the Declaration of Helsinki and complied with the International Conference on Harmonisation, Good Clinical Practice, and applicable regulatory requirements.

### Provenance

Freely submitted; externally peer reviewed.

### Competing interests

Marc Russo, Mark Bloch, and Fred de Looze have declared no competing interests. Christopher Morris and Adrian Shephard are employees of Reckitt Benckiser Healthcare International Ltd.

### Trial registration

ACTRN12609000329268.

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