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Onset of analgesia by a topically administered flurbiprofen lozenge: a randomised controlled trial using the double stopwatch method

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Abstract

Background: The double stopwatch (DSW) method for determining the onset of analgesic activity has been implemented extensively by investigators studying orally administered drugs.

Objective: The aim of this randomised, placebo-controlled trial was to use the DSW method to determine the time to onset of analgesia of a single dose of a topically administered non-steroidal anti-inflammatory drug, flurbiprofen 8.75 mg lozenge.

Methods: Adults with acute sore throat (n = 122) were examined to confirm the presence of tonsillopharyngitis (Tonsillo-Pharyngitis Assessment) and sore throat pain of at least moderate intensity (≥6 on a 0–10 Sore Throat Scale). Lozenges containing flurbiprofen 8.75 mg or inert ingredients (identically flavoured) were administered under double-blind conditions in the clinic while patients assessed pain and pain relief over 3 hours. Onset of analgesia was determined using the DSW method and reported as the Kaplan–Meier median time to meaningful relief. The median time to first perceived relief was also documented.

Results: About 78% of flurbiprofen-treated patients reported meaningful pain relief compared with 48% of placebo-treated patients ($p < 0.01$); median time to meaningful relief for flurbiprofen-treated patients was 43 minutes (placebo-treated patients were right-censored due to non-responsivity; $p = 0.01$). Median time to first perceived pain relief was 11 minutes for flurbiprofen-treated patients and 19 minutes for placebo-treated patients ($p = 0.03$). Flurbiprofen lozenge was well tolerated, with no serious adverse events occurring and no patient discontinuing due to an adverse event.

Conclusion: These results indicate that the DSW method can be successfully applied to the evaluation of the onset of action of a locally administered analgesic in patients with acute sore throat, demonstrating that the onset of action (time to meaningful pain relief) of flurbiprofen lozenge was <45 minutes.

Keywords

Double stopwatch method, topical analgesia, onset of action, flurbiprofen, pharyngitis, sore throat

Introduction

The double stopwatch (DSW) method has been used to determine the onset of action of analgesics delivered in solid dosage and parenteral forms in a variety of pain models, including oral surgery, bunionectomy, tension-type headache and sore throat.[1–6] Subjects are instructed to depress a stopwatch when they perceive any pain relief and a second stopwatch when they

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experience what they consider to be meaningful pain relief. The DSW method thus provides discrete times for two patient-reported assessments indicating the onset of analgesia.

Sore throat pain is an established acute pain model that has been studied extensively for several decades[7–9] and is well characterised in terms of study design, the objective confirmation of pharyngitis (the Tonsillo-Pharyngitis Assessment (TPA)) and the rating scales used to evaluate outcomes.[4,10–14] This model has been used to assess the efficacy of flurbiprofen 8.75 mg lozenge[13,14] and flurbiprofen 8.75 mg spray,[15] developed for the over-the-counter symptomatic relief of sore throat.

The onset of analgesia for topically administered flurbiprofen has been examined in patients with painful pharyngitis from a pharmacodynamic perspective using frequent measurements of sore throat pain intensity following the first dose.[13] The aim of this study, which follows a small pilot investigation,[16] was to determine the onset of analgesia following the first dose of the flurbiprofen lozenge using the DSW method. This is thought to be the first fully documented study utilising the DSW method to measure the onset of a topically applied sore throat treatment.

Methods

Study design

This was a phase 3, randomised, double-blind, single-dose, placebo-controlled study conducted at a university health centre in Connecticut, United States, between 9 September 2013 and 24 April 2014, funded by Reckitt Benckiser and registered on the clinicaltrials.gov registry (NCT01986361). The study received prior ethical approval from the University's Institutional Review Board and was conducted according to International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and principles of the Declaration of Helsinki, as referenced in EU Directive 2001/20/EC. The study also complied with the US GCP regulations in the Code of Federal Regulations. Patients were recruited from the health centre, and written informed consent was obtained from each subject prior to study participation.

Study population

Adult male and female patients (≥18 years of age) were eligible for inclusion in the study if they had a complaint of sore throat within the past 4 days. To establish disease status at baseline, physical evidence of tonsillopharyngitis was required, based on a score ≥5 on the 21-point TPA (Table 1). The TPA examines seven objective findings indicative of pharyngeal inflammation, each rated on a semi-quantitative 0–3 scale, which added together makes the TPA score.[4] The extent of pharyngeal inflammation was assessed using the Practitioner's Assessment of Inflammation (PAIN), a four-category (none, mild, moderate or severe) scale.[14] To confirm the infectious origin of pharyngitis, patients were eligible only if they reported at least one other symptom of upper respiratory tract infection (URTI) in the previous 24 hours on the URTI Questionnaire, an index consisting of nominal scales for common symptoms of URTI.[14] A throat culture was obtained to identify a bacterial aetiology of sore throat (i.e. Group A or C streptococcal infection). Eligible patients were required to report moderate or severe throat pain (on the categorical Throat Pain Scale (TPS)) confirmed by a rating ≥6 on the 11-point Sore Throat Scale (STS).[12] As a linear measurement of pain intensity, patients also rated throat pain on the 100-mm visual analogue Sore Throat Pain Intensity Scale (STPIS).[10]

Major exclusion criteria included the use of antibiotics for an acute disease in the 24 hours before randomisation; any sustained release analgesic within 12 hours of administration of study medication; any cold medications, analgesic or antipyretic within 4 hours of administration of study medication; and any lozenge, spray, cough drop or menthol-containing products within 2 hours of administration of study medication. Patients were also excluded if they had any evidence of mouth breathing or coughing that caused or worsened throat soreness. Standard warnings and contraindications for non-steroidal anti-inflammatory drugs (NSAIDs) were also used to assess patient eligibility.

Study medications and randomisation

Patients meeting eligibility criteria were randomised in a ratio of 5:1 to treatment with one flurbiprofen 8.75 mg lozenge or one placebo lozenge (matched for appearance, shape, size, colour, taste and consistency). All study treatments were prepared and randomised by Reckitt Benckiser LLC according to a computer-generated randomised schedule, and patients were allocated a unique patient number in numerical sequence. Because the placebo lozenge was included to achieve blinding, fewer patients were allocated to placebo. Patients were instructed to suck (not chew, bite or swallow) the allocated lozenge, occasionally moving it from one side of their mouth to the other until fully dissolved. Patients were not allowed to take anything by mouth during the 3-hour study period with the exception of rescue analgesia (acetaminophen 650 mg), if needed. They were observed over the study period at the research centre while the investigator and research nurses conducted the assessments.

Table 1. Tonsillo-Pharyngitis Assessment (TPA).

Item	0 points	1 point	2 points	3 points
Oral temperature	≤98.6°F	98.7–98.9°F	99.0–99.9°F	≥100.0°F
Oropharyngeal colour	Normal/pink	Slightly red	Red	Beefy red
Size of tonsils	Normal/absent	Slightly enlarged	Moderately enlarged	Much enlarged
Number of oropharyngeal enanthems (vesicles, petechiae or exudates)	None	Few	Several	Many
Largest size of anterior cervical lymph nodes	Normal	Slightly enlarged	Moderately enlarged	Much enlarged
Number of anterior cervical lymph nodes	Normal	Slightly increased	Moderately increased	Greatly increased
Maximum tenderness of some anterior cervical lymph nodes	Not tender	Slightly tender	Moderately tender	Very tender

Outcome measures

Following the standard DSW methodology, two stopwatches were started when the patient first placed the randomly assigned lozenge in his or her mouth. Patients were instructed to depress the first stopwatch when they first perceived any pain relief and to depress the second stopwatch when they experienced relief that was meaningful to them ('Stop the second stopwatch when the sore throat pain relief is meaningful to you. This does not mean you feel completely better, although you might, but when you feel relief of throat pain that is meaningful to you'). Time to meaningful pain relief was the primary outcome. Secondary outcome measures included time of first perceived pain relief, and time of first perceived pain relief that was subsequently confirmed by meaningful pain relief (on the second stopwatch).

Sore throat pain intensity was measured on the STS every 5 minutes during the first hour and every 10 minutes during the second and third hours of the study, and the STPIS was repeated at 1 hour, 2 hours, 3 hours and at the time the second stopwatch was stopped (indicating meaningful relief). All patients with streptococcal infection were treated with an appropriate antibiotic upon receipt of culture results. The safety of the study medication was assessed throughout the 3-hour study period with respect to the nature and frequency of adverse events, which were classified according to MedDRA® Version 15.1.

Statistical analyses

Based on results from a pilot DSW study[16] to develop methodology, 100 patients randomised to flurbiprofen (and 20 to placebo) were considered sufficient for the study to have >90% power to demonstrate that the flurbiprofen lozenge provided meaningful pain relief (using the upper limit of the two-sided Kaplan–Meier (KM) 95% confidence interval (CI) for an estimated 17-minute median time to meaningful pain relief).

Analyses were conducted on the entire intent-to-treat population, and included patients who were randomised, took the study medication and had at least one post-treatment efficacy assessment. Subgroup analyses were also conducted for patients with baseline STS of >7 and TPA of >7 and for patients with culture-proven streptococcal infection.

The KM median time to meaningful pain relief was calculated with two-sided 95% CI. For patients who did not achieve meaningful pain relief within 3 hours, times were right-censored to 3 hours. The upper limit of the 95% CI for the median time to meaningful pain relief provided evidence of the time of onset by the flurbiprofen lozenge. These analyses were also conducted for the time to first perceived pain relief and the time to first perceived pain relief confirmed by meaningful pain relief. Log-rank tests were used to determine differences between flurbiprofen and placebo treatments for these endpoints and for the subgroup analyses. The proportion of patients achieving these endpoints over 3 hours was analysed using Fisher's exact test.

The Wilcoxon signed-rank test was used to analyse reduction from baseline in STS, and *t* test was used for STPIS.

Results

Patient disposition

In total, 101 patients were randomised to flurbiprofen 8.75 mg lozenge and 21 to placebo, all of whom completed the 3-hour study (Figure 1). Demographics and baseline characteristics were similar between the two treatment groups (Table 2). Patients had an average age of 19.5 years and most were women. Forty-two per cent of the patients had baseline STS >7 and TPA >7. Group A or Group C streptococcal infection was detected by throat culture in 34% of all patients.

Onset of analgesia – overall study population

Over the 3-hour study period, 78% of flurbiprofen-treated patients had meaningful pain relief, compared

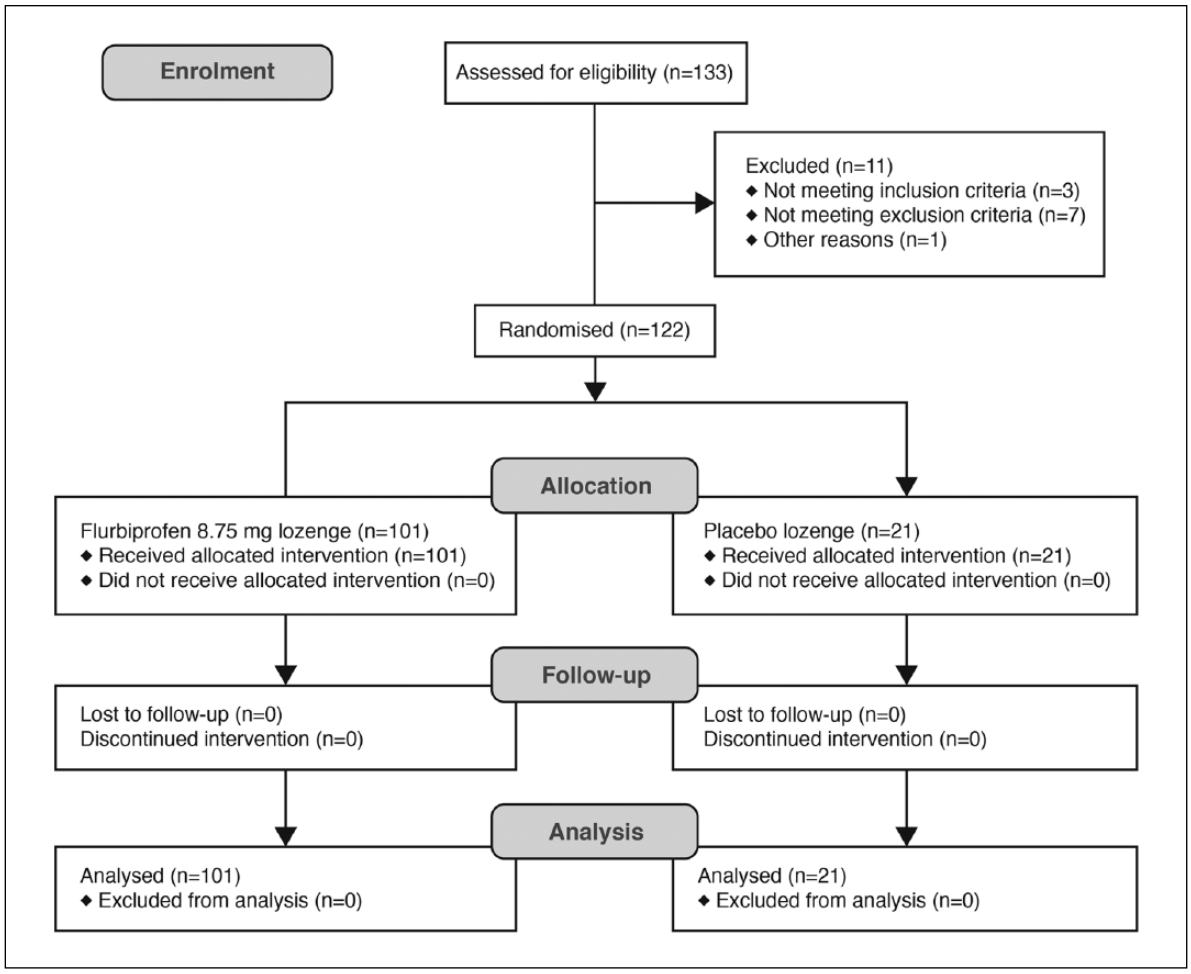

Figure 1. Patient disposition.

with 48% of placebo-treated patients ($p < 0.01$; Figure 2). Meaningful pain relief was achieved by 32% (32/101) of flurbiprofen-treated patients within 30 minutes and by 66% (67/101) within 60 minutes; 22 (21.8%) patients were right-censored. In comparison, 19% (4/21) and 43% (9/21) of placebo-treated patients reported meaningful pain relief within 30 and 60 minutes, respectively. Fifty-two per cent of placebo-treated patients (11/21) did not experience meaningful relief within 3 hours and were right-censored.

The median time to meaningful pain relief for flurbiprofen-treated patients was 43 minutes (95% CI: 36.4–49.4 minutes), significantly different from placebo-treated patients ($p = 0.01$).

At 45 minutes, the scheduled pain assessment time which was closest to the median time to meaningful pain relief (43 minutes) reported by flurbiprofen-treated patients, there was an absolute mean 2.2-point reduction from baseline on the 11-point STS for flurbiprofen-treated patients and a 1.2-point reduction from baseline for placebo-treated patients. At 43 minutes, there was a 42% mean reduction in throat pain as measured on the STPIS, which was not significantly different from the mean 48% pain intensity difference in placebo-treated patients ($p = 0.38$). This corresponded with an absolute change of -30.7 ± 13.0 mm from baseline (mean ± SD) at 43 minutes for flurbiprofen-treated patients and -33.1 ± 19.3 mm for placebo-treated patients ($p = 0.61$).

Median time to first perceived pain relief confirmed by meaningful pain relief for flurbiprofen-treated patients was 13 minutes (95% CI: 8.6–16.6 minutes), which was significantly different from placebo-treated patients ($p = 0.02$).

First perceived relief was achieved by 97% of flurbiprofen-treated patients and 76% of placebo-treated patients over 3 hours ($p < 0.01$). Median time to first perceived relief for flurbiprofen-treated patients was 11 minutes (95% CI: 7.6–14.3 minutes) compared with 19 minutes (95% CI: 4.8–30.3 minutes) for placebo-treated patients ($p = 0.03$). About 85% (86/101) of flurbiprofen-treated patients first perceived pain relief within 30 minutes and 97% (98/101) within 60 minutes. These outcomes compared with 67%

Table 2. Patient demographics and baseline characteristics.

Characteristic	Flurbiprofen 8.75 mg (n = 101)	Placebo (n = 21)	Overall (n = 122)
Female, n (%)	58 (57)	13 (62)	71 (58)
Mean age (SD) [range], years	19.5 (2.02) [18–33]	19.6 (1.36) [18–22]	19.5 (1.92) [18–33]
Ethnicity, n (%)			
Caucasian	94 (93)	19 (90)	113 (93)
Asian	2 (2)	0 (0)	2 (2)
Black or African American	3 (3)	2 (10)	5 (4)
Multiracial	2 (2)	0 (0)	2 (2)
TPA total score, mean (SD) [range]	9.8 (2.57) [5.0–15.0]	10.3 (2.82) [6.0–15.0]	9.9 (2.61) [5.0–15.0]
PAIN, n (%)			
No inflammation	0	0	0
Mild inflammation	37 (36.6)	7 (33.3)	44 (36.1)
Moderate inflammation	58 (57.4)	14 (66.7)	72 (59.0)
Severe inflammation	6 (5.9)	0	6 (4.9)
TPS, n (%)			
Moderate	68 (67.3)	8 (38.1)	76 (62.3)
Severe	33 (32.7)	13 (61.9)	46 (37.7)
STS score, mean (SD) [range]	7.4 (0.97) [6.0–10.0]	7.3 (1.02) [6.0–9.0]	7.4 (0.98) [6.0–10.0]
STPIS, mean (SD), mm	73.8 (9.8)	73.8 (9.6)	73.8 (9.7)
Patients with STS > 7 and TPS > 7, n (%)	43 (42.6)	8 (38.1)	51 (41.8)
Patients positive for Strep A, n (%)	15 (15)	3 (14)	18 (15)
Patients positive for Strep C, n (%)	19 (19)	5 (24)	24 (20)

PAIN: Practitioner's Assessment of Inflammation; SD: standard deviation; Strep A: Group A streptococcus; Strep C: Group C streptococcus; STPIS: Sore Throat Pain Intensity Scale; STS: Sore Throat Scale; TPA: Tonsillo-Pharyngitis Assessment; TPS: Throat Pain Scale.

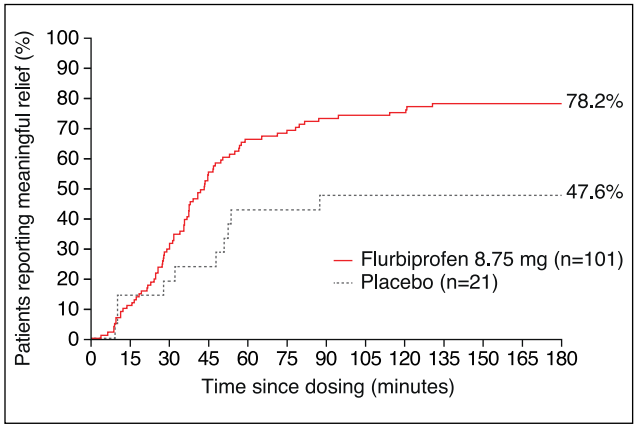

Figure 2. Percentage of patients reporting meaningful pain relief.

(14/21) and 76% (16/21) of placebo-treated patients, respectively, with 5 (24%) of placebo-treated patients right-censored.

Onset of analgesia – subgroup of patients with baseline STS >7 and TPA >7

In the subgroup of patients (42%) with baseline STS >7 and TPA >7, meaningful relief was reported by 70% of flurbiprofen-treated patients and 13% of placebo-treated patients ($p < 0.01$; Figure 3). Median time to meaningful relief for flurbiprofen-treated patients was 47 minutes (95% CI: 35.4–78.1), which was significantly different from placebo ($p = 0.01$). First perceived relief was achieved by 95% of flurbiprofen-treated patients with baseline STS >7 and TPA >7, compared with 63% of placebo-treated patients ($p = 0.02$). Median time to first perceived relief was 16 minutes (95% CI: 7.3–25.2 minutes) for flurbiprofen-treated patients with baseline STS >7 and TPA >7, which was significantly different from placebo (29 minutes, $p = 0.04$).

Onset of analgesia – subgroup of patients with streptococcal infection

In patients with Group A or C streptococcal throat infection, 82% of flurbiprofen-treated patients reported meaningful pain relief compared with 63% of placebo-treated patients ($p = 0.34$; Figure 4). Median time to meaningful relief was 41 minutes (95% CI: 29.7–47.2 minutes) for flurbiprofen-treated patients with streptococcal infection, not significantly different from placebo (52 minutes, $p = 0.18$). Among flurbiprofen-treated patients, there was no significant difference in the

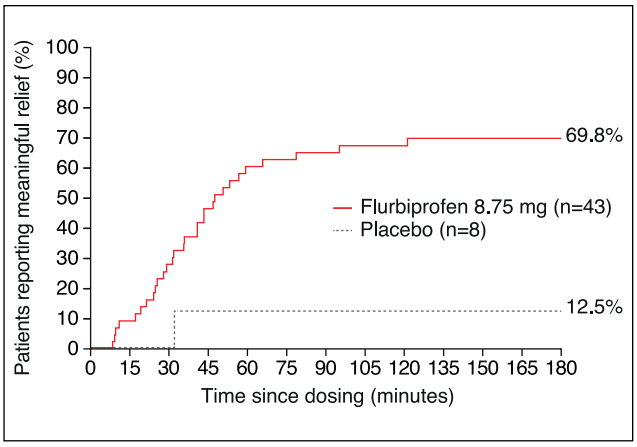

Figure 3. Percentage of patients with baseline STS >7 and TPA >7 reporting meaningful pain relief.

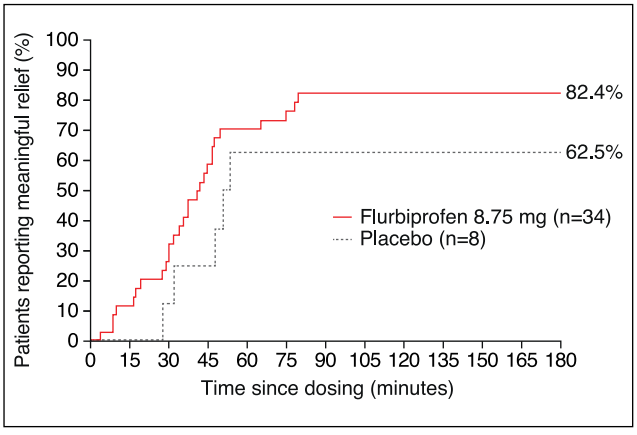

Figure 4. Percentage of patients with pharyngitis due to streptococcal throat infection reporting meaningful pain relief.

median time to meaningful relief for patients with or without Group A or C streptococcal throat infection ($p = 0.39$). All flurbiprofen-treated patients with Group A or C streptococcal throat infection reported first perceived pain relief, as did 88% of placebo-treated patients ($p = 0.19$). Median time to first perceived pain relief by flurbiprofen-treated patients with Group A or C streptococcal throat infection was 9 minutes (95% CI: 3.5–22.4 minutes), not different from placebo (7 minutes, $p = 0.84$).

Safety and tolerability

Treatment-emergent adverse events occurred in 11 (9%) patients, all but one in the flurbiprofen treatment group ($p = 0.69$ versus placebo; Table 3). Only two adverse events (abdominal discomfort and throat irritation) were considered possibly or probably related to (flurbiprofen) study medication. No serious adverse events occurred and no patients discontinued the study due to adverse events.

Discussion

This study demonstrated the onset of analgesia of low-dose flurbiprofen from a topically administered lozenge in patients with painful pharyngitis using the DSW method.

This identification of the onset of analgesia attributable to a topically administered lozenge is complicated by the demulcent effect[17] of the sugary vehicle base of the lozenge itself. Demulcency from the lozenge base was demonstrated in this study using the DSW method, with 76% of patients taking the placebo lozenge first perceiving relief of throat pain beginning at 19 minutes. However, as measured by the second stopwatch, for 52% of placebo-treated patients, the extent of pain relief was not meaningful.

In contrast, the DSW method was sensitive to the pharmacological effect of flurbiprofen in the active lozenge, identifying a median time of first perceived relief less than 15 minutes and meaningful relief at 43 minutes. In keeping with previous research on how to interpret meaningful quantitative changes in pain intensity categories,[18] we characterised the changes observed in this trial as clinically meaningful according to published criteria based on the scalar instruments we used. At the median time of meaningful relief (as defined by the DSW technique), flurbiprofen-treated patients reported 42% mean reduction in pain intensity on the linear 100-mm STPIS, indicative of criteria for 'much improvement'[19] and approaching 'definite improvement'[20] of acute pain. The DSW results for meaningful relief reported by flurbiprofen-treated patients were also substantiated by the patient-reported outcome on the 11-point numerical pain intensity rating scale (STS) at 45 minutes (the closest time point to the median time of meaningful relief detected using the DSW method): flurbiprofen-treated patients recorded a mean 2.2-point reduction at 45 minutes. This outcome is also clinically significant, because a greater than 2-point reduction in pain measured on a numerical rating scale indicates a 'clinically important' change.[21,22]

These different methods of detecting pharmacological activity demonstrated the onset of a clinically meaningful effect of the flurbiprofen 8.75 mg lozenge and suggest that linear and numerical rating scales can be used alongside the DSW method to detect the effect of drugs at the time of onset. As a complement to the detection of the time of meaningful relief on the second stopwatch of the DSW method, the concurrently administered linear rating scale, in particular, provides a direct measurement of the per cent change in pain intensity at the time of meaningful relief.

Table 3. Summary of adverse events.

Adverse event	Flurbiprofen 8.75 mg (n = 101)	Placebo (n = 21)	Overall (n = 122)
Patients with adverse events, n (%)	10 (10)*	1 (5)	11 (9)
Gastrointestinal disorders, n (%)	4 (4)	0 (0)	4 (3)
Abdominal discomfort	1 (1)	0 (0)	1 (1)
Diarrhoea	1 (1)	0 (0)	1 (1)
Nausea	2 (2)	0 (0)	2 (2)
Nervous system disorders, n (%)	2 (2)	1 (5)	3 (2)
Dizziness	1 (1)	0 (0)	1 (1)
Headache	1 (1)	1 (5)	2 (2)
Respiratory, thoracic and mediastinal disorders, n (%)	3 (3)	0 (0)	3 (2)
Cough	1 (1)	0 (0)	1 (1)
Throat irritation	1 (1)	0 (0)	1 (1)
Tonsillar hypertrophy	1 (1)	0 (0)	1 (1)
General disorders and administration site conditions, n (%)	2 (2)	0 (0)	2 (2)
Pyrexia	2 (2)	0 (0)	2 (2)
Infections and infestations	2 (2)	0 (0)	2 (2)
Conjunctivitis infective	1 (1)	0 (0)	1 (1)
Laryngitis	1 (1)	0 (0)	1 (1)

*p = 0.69 versus placebo.

An exploratory endpoint of this study potentially supports an alignment between DSW findings and results on standard pain rating scales. Within the conventional construct of a randomised controlled trial with regularly scheduled pain assessments, we assessed the time to the first reduction in STS, which was later confirmed by at least 20% pain reduction on the STPIS. This endpoint thus served as a surrogate in a randomised controlled trial of the DSW endpoint of first perceived relief that is later confirmed by meaningful relief. The observed time of this exploratory endpoint (15 minutes, reported by 81% of flurbiprofen-treated patients) was very similar to the DSW-measured endpoint (13 minutes). However, this observation should be viewed only as exploratory because, like other between-treatment comparisons, definitive differentiation from placebo was not possible given the small sample size of the placebo treatment group.

Although not directly comparable with results from other sore throat studies that employed the DSW method to identify the onset of action of systemically administered analgesic tablets, the median times to meaningful relief observed for patients treated with low-dose flurbiprofen in this study (43 minutes in the overall population, 47 minutes in patients with baseline STS >7 and TPA >7, 41 minutes in patients with streptococcal throat infection) correspond with the median times to meaningful pain relief reported for systemic acetylsalicylic acid 1000 mg (48 minutes) and acetaminophen 1000 mg (40 minutes) in patients with sore throat.[6] This consistency of onset results based on the DSW method lends confidence to the findings in this study.

The findings in this study that demonstrated onset of clinically significant analgesia for patients with and without streptococcal pharyngitis are informative from another (clinical and epidemiologic) perspective. They confirm previous reports of the efficacy of low-dose flurbiprofen lozenge in patients with and without sore throat due to streptococcal infection.[7,8,13,23,24] These findings also justify the provision of only symptomatic treatment for most patients with sore throat until culture results indicate a bacterial aetiology. Despite its largely viral aetiology,[25] acute pharyngitis frequently results in antibiotic use following presentation at primary care settings.[26,27] A non-antibiotic, symptomatic management strategy[28,29] allows practitioners to reserve antibiotics for patients who are diagnosed with Strep A infection[30] or severe Strep C,[23] who have risk factors for complications,[31] or who are systemically unwell. As observed in this study implementing the DSW technique to demonstrate the onset of relief for sore throat, symptomatic treatment while awaiting throat culture results could help avoid inappropriate antibiotic use.

There is one notable shortcoming of this study. The placebo treatment group was included in the design of this study to maintain blinding of study treatments. As a result, the placebo treatment group had a small

sample size, which presents limitations when assessing the efficacy of the active treatment compared with placebo. Even though differentiation of active drug from placebo was observed in this study, to avoid the risk of under-observing pharmacologic effects, future studies utilising the DSW method to examine the onset of a topically administered analgesic should include a placebo treatment group that is comparable in size to the active treatment.

In summary, this study on a topically administered analgesic successfully utilised the DSW method to demonstrate that flurbiprofen 8.75 mg lozenge provides fast and meaningful pain relief for sore throat due to acute tonsillopharyngitis.

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Author contributions

All authors have contributed substantially to the study reported in this manuscript and to the development of the manuscript. All authors contributed to the study concept, design and interpretation of the results. Celerion (Belfast, Northern Ireland, UK) performed the statistical analyses. All authors were involved in the conduct of the study and acquisition of data. All authors have reviewed and approved the manuscript.

Conflict of interest

A.S. and T.S. are employees of Reckitt Benckiser Healthcare Ltd, UK, as was S.A. at the time of preparation of the manuscript. B.S., M.B.L. and E.S. (at Schachtel Research Company) received a research grant from Reckitt Benckiser to design and conduct the study.

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