ORIGINAL RESEARCH

Improvements in throat function and qualities of sore throat from locally applied flurbiprofen 8.75 mg in spray or lozenge format: findings from a randomized trial of patients with upper respiratory tract infection in the Russian Federation

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Objective: To assess the speed of relief provided by flurbiprofen 8.75 mg spray and lozenge and their effect on many of the different qualities and characteristics of throat pain and discomfort, and the many articulations of the broad term "sore throat" (ST).

Patients and methods: Four hundred and forty adults with recent-onset, moderate-to-severe ST due to upper respiratory tract infection (URTI) were randomized to a single dose of either flurbiprofen 8.75 mg spray (n=218) or flurbiprofen 8.75 mg lozenge (n=222). Throat swabs for bacterial culture were taken at baseline. ST relief was assessed at 1 minute, 1 and 2 hours post-dose using the Sore Throat Relief Rating Scale. The change from baseline at 1 and 2 hours post-dose in difficulty swallowing and swollen throat was assessed using the difficulty swallowing scale and the swollen throat scale, respectively. Patients' experience of URTI symptoms was assessed using a URTI questionnaire at baseline and 2 hours post-dose. The change in Qualities of Sore Throat Index, a 10-item index of qualities of ST, from baseline at 2 hours post-dose was also measured.

Results: ST relief was evident in the spray and the lozenge treatment groups at 1 minute, 1 and 2 hours post-dose ($P>0.05$). In both groups, scores for difficulty swallowing and swollen throat significantly improved at 1 and 2 hours post-dose compared with baseline. At 2 hours post-dose, the number of patients experiencing URTI symptoms that can be attributed to or associated with ST decreased relative to baseline. The mean change from baseline to 2 hours post-dose for each individual score on the Qualities of Sore Throat Index showed significant improvements for flurbiprofen spray and lozenge (all $P<0.0001$).

Conclusion: Non-inferiority was established, and flurbiprofen spray and lozenge provided effective relief from ST pain and many of the other commonly reported qualities of ST.

Keywords: flurbiprofen, non-inferiority, spray, lozenge

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Introduction

Sore throat (ST) is a symptom of pharyngeal inflammation[1,2] that often results from an upper respiratory tract infection (URTI).[2] Patients reporting to the primary care for ST often complain of odynophagia, throat swelling, and dysphagia;[3] however, beyond these complaints, patients may report a broad range of other sensory, functional, and

affective qualities of ST pain.[3–5] These qualities include burning, rawness, dryness, an irritated/scratchy/tickly sensation, tightness, the feeling of having a lump in the throat, a husky/hoarse voice, and agonizing pain.[3,5] Some of these ST qualities are rated by patients as more painful than others; for example, a dry or scratchy, tickly, and itchy throat is associated with less pain and discomfort than a swollen, tight throat, and stabbing, sharp pain.[4] The wide variety of different patient-reported ST qualities reflects a number of factors, including the probable cause of ST, such as URTI,[6] the individual's immune response and pain thresholds,[7] and social and environmental influences.[1,8]

The availability of effective symptomatic relief is an important factor in meeting patients' needs and avoiding unnecessary use of antibiotics[9,10] which are frequently inappropriate for ST and do not provide relief from painful symptoms. Medicinal format is a driver of patient choice[6] and, particularly for ST, different formats can provide different experiences[11–15] with local treatments often containing a lower dose of active ingredient than systemic analgesics, and may therefore be associated with a reduced risk of adverse events.[14]

The non-steroidal anti-inflammatory drug flurbiprofen is one of the very few examples available of a locally delivered, traditional analgesic and anti-inflammatory agent.[16,17] Lozenges containing a low dose of 8.75 mg flurbiprofen have a good safety profile and are proven to be effective in relieving various characteristics of ST.[5,11,18,19] However, the recently developed, innovative spray formulation containing the same low flurbiprofen dose of 8.75 mg provides patients with ST with another treatment option.[12]

The primary objective of a recent, randomized, non-inferiority, active comparator study was to assess the efficacy of flurbiprofen 8.75 mg delivered as a spray or lozenge in patients with ST due to URTI.[20] Here, we focus on the speed of relief provided by flurbiprofen 8.75 mg spray and lozenge in that study, as well as the improved throat function resulting from treatment. This analysis concentrates on the effect of flurbiprofen 8.75 mg spray and lozenge on many of the different qualities and characteristics of ST pain and discomfort, and the many articulations of the broad term "ST".

Patients and methods
Study design
This randomized (1:1), single-dose, double-dummy, double-blind, parallel group, active-controlled, non-inferiority, multicenter study was conducted at 16 investigational centers in the Russian Federation between November 28, 2014 and November 14, 2015. The study was performed in accordance with all applicable Russian regulatory guidelines, in addition to the Declaration of Helsinki (EU Directive 2001/20/EC) and the International Conference on Harmonisation Good Clinical Practice guidelines. The study was also approved by the independent ethics committees at each investigational site and the Ethics Council at the Russian Federation Ministry of Healthcare. All participants in the trial provided written informed consent. The methodology for this trial was reported previously,[20] and is briefly described below.

Study population
Adults with moderate or severe ST due to URTI (onset within ≤4 days) were included, based on the inclusion and exclusion criteria reported previously.[20] Briefly, patients had objectively confirmed ST and at least one symptom of URTI, and did not have purulent plaques on the tonsils, a severe cough, or elevated temperature (≥38°C).

Study medications
Patients were block randomized to receive either a single dose of flurbiprofen 8.75 mg spray (Reckitt Benckiser, Hull, UK) plus one placebo lozenge or one flurbiprofen 8.75 mg lozenge (Reckitt Benckiser) plus a single dose of placebo spray as described previously.[20]

Study assessments
At baseline, patients were asked to swallow and then indicate the degree of difficulty with swallowing on the Difficulty Swallowing Scale (DSS), a 100 mm visual analog scale where 0="not difficult" and 100="very difficult". They were also asked to swallow and indicate how swollen their throat felt on the Swollen Throat Scale (SwoTS), a 100 mm visual analog scale where 0="not swollen" and 100="very swollen". Patients were also asked to identify all current symptoms and symptoms experienced over the last 24 hours from a list of 39 common (plus "other") symptoms using the URTI questionnaire, an index consisting of nominal scales for common symptoms of URTI (Table 1). In addition to the symptoms that can be ascribed to URTI, the URTI questionnaire also includes symptoms that can be attributed to or associated specifically with ST (e.g., throat tickle, tender/swollen neck glands, coughing, throat clearing, post-nasal drip; Table 1).

Other baseline assessments included an analysis based on the Qualities of Sore Throat Index (QuaSTI), a 10-item index of qualities of ST (agonizing, burning, difficult to swallow, dry, husky/hoarse voice, irritated/scratchy, like a lump in the throat, raw, swollen, tight) rated on an ordinal scale of 0–10, where 0="not at all" and 10="a lot", which was developed

Table 1 The URTI questionnaire

What are your symptoms now (check all that apply)?			
☐ Runny nose	☐ Garbled speech	☐ Headache	☐ Head fullness
☐ Stuffy nose	☐ Sneezing	☐ **Throat clearing**	☐ **Coughing**
☐ Earache	☐ **Sore throat**	☐ Wheezing	☐ Chest tightness
☐ **Throat tickle**	☐ Mouth breathing	☐ Clogged ears	☐ Phlegm
☐ Ear fullness	☐ Crackling ears	☐ Burning ears	☐ Sweating
☐ Achiness	☐ **Post-nasal drip**	☐ Loss of appetite	☐ Inability to sleep
☐ Drowsy	☐ Lack of energy	☐ Sinus pressure	☐ Sinus pain
☐ Heartburn	☐ Watery eyes	☐ Acid indigestion	☐ Nausea
☐ Pressure around the eyes	☐ Upset stomach	☐ Feverish	☐ Chills
☐ Other (specify)	☐ **Tender neck glands**	☐ **Swollen neck glands**	☐ Dizzy

Notes: Symptoms in bold represent symptoms that are attributable to, or associated with, sore throat and present in >10% of patients. All other symptoms are those that can be generally ascribed to URTI.
Abbreviation: URTI, upper respiratory tract infection.

by Schachtel et al.[5] The Clinical Assessment of Strep Throat (CAST) was also performed at baseline: based on the patient's history, symptoms, and physical findings, investigators were asked to make a clinical judgment on the likelihood that the patient had Group A beta-hemolytic *Streptococcus* or "Strep throat" using a 4-point categorical scale (unlikely, uncertain, likely, very likely). Throat swabs for bacterial culture were also taken at baseline to identify those patients with ST due to streptococcal infection (Group A or C); swabs were processed in a central laboratory (INVITRO Ltd, Moscow, Russia) and the results were available after the completion of the efficacy evaluation.

Endpoints

ST relief was assessed at 1 minute (following the 10-minute interval allowed for the lozenge to dissolve), 1 and 2 hours post-dose using the Sore Throat Relief Rating Scale (STRRS), a 7-point categorical scale with the following response options: 0="no relief", 1="slight relief", 2="mild relief", 3="moderate relief", 4="considerable relief", 5="almost complete relief", and 6="complete relief". Total sum of pain relief ratings over 2 hours (area under the change from baseline curve: $TOTPAR_{0–2\,hours}$) was also evaluated.

Other endpoints were change from baseline at 1 and 2 hours in the DSS (DSS 1 hour, DSS 2 hours) and SwoTS (SwoTS 1 hour, SwoTS 2 hours); the area under the change from baseline curve over 2 hours for the DSS (DSS $AUC_{0–2\,hours}$) and SwoTS (SwoTS $AUC_{0–2\,hours}$); URTI questionnaire at 2 hours post-dose (patients were asked to identify all current symptoms); scores for each of the 10 individual QuaSTI components, the sum score for all QuaSTI items, and qualities split into three categories (sensory qualities: burning, raw, like a lump in the throat, dry, tight, irritated/scratchy, swollen; functional qualities: husky/hoarse voice,

difficulty swallowing; affective descriptor: agonizing) at 2 hours post-dose; and patient's global evaluation of study treatment (GLOBAL) at 2 hours post-dose, using a 5-point categorical scale (poor, fair, good, very good, excellent).

Statistical analyses

The null hypothesis at all times was the equality of both treatments. The sample size was calculated as described previously.[20] Efficacy was evaluated in the per protocol set (the primary analysis population, as this was a non-inferiority study) and the full analysis set (based on the intent-to-treat principle). The safety set included all patients who took the study medication.

Data for ST relief (on the STRRS) at 1 minute were summarized descriptively, and data at 1 and 2 hours were analyzed using the Mann–Whitney *U* test. For difference from baseline at 1 and 2 hours post-dose in DSS (DSS 1 hour, DSS 2 hours) and SwoTS (SwoTS 1 hour, SwoTS 2 hours), least squares (LS) means and mean square error were compared using analysis of covariance (ANCOVA) with the relevant baseline value as the covariate, fixed effects for treatment group and treatment sequence, and a random effect for center. $TOTPAR_{0–2\,hours}$ was analyzed using the same ANCOVA model, but with baseline values for ST pain intensity as a covariate; AUC in $TOTPAR_{0–2\,hours}$, $DSS_{0–2\,hours}$, and $SwoTS_{0–2\,hours}$ were analyzed using the trapezoid method using the same ANCOVA model, but with the relevant baseline values as the covariate.

For every symptom of the URTI questionnaire at screening and at 2 hours post-dose, the crosstabs with Fisher's exact test were performed for both treatment groups. Changes in symptoms between baseline and 2 hours post-dose (Resolved, Absent, Still Present, Developed) were compared for each treatment group using McNemar's test; additionally, every

symptom at 2 hours post-dose was assessed using a logistic regression model with baseline value and treatment as fixed effects. The results reported here focus on those symptoms that are associated with ST.

For the QuaSTI at 2 hours post-dose, the change from baseline in each of the 10 items on the QuaSTI (from agonizing to tight) and for the three categories of qualities was calculated for each subject per treatment. Similarly, the sum for scores was calculated across all items and summarized using descriptive statistics. One-sample Student's *t*-test was used to assess if the mean change was statistically significantly different from zero. Patient's global evaluation of study treatment (GLOBAL) at 2 hours post-dose was analyzed using the Mann–Whitney *U* test. Two-sided statistical tests and a 5% significance level were used.

Results

Patient disposition

A total of 441 patients were screened and 440 were enrolled and randomized into the study (flurbiprofen 8.75 mg spray, n=218; flurbiprofen 8.75 mg lozenge, n=222; Figure 1). In the flurbiprofen 8.75 mg spray group, one patient was withdrawn due to a protocol deviation.

Baseline demographics and characteristics

The demographics and baseline characteristics of the treatment groups were well balanced (Tables 2–4). The majority of participants were Caucasian, and the most commonly

reported URTI symptoms at baseline in both treatment groups included achiness, headache, lack of energy, ST, tender neck glands, throat tickle, and throat clearing, as well as coughing, swollen glands, and post-nasal drip. Most patients reported moderate pain on the Throat Pain Scale (137/217 [63.1%] patients in the flurbiprofen spray group and 126/222 [56.8%] patients in the flurbiprofen lozenge group).

Results of the CAST showed in total that one patient was considered "very likely" and 78 patients were considered "likely" (18.0%) to have Strep infection, while Strep throat was considered "uncertain" in 123 patients (28.4%) and unlikely in 231 (53.3%) patients. Throat culture results provided a definitive diagnosis of Strep A or C infection in 13/201 (6.5%) patients from the flurbiprofen spray group and 9/210 (4.3%) patients from the flurbiprofen lozenge group. Overall, the sensitivity and specificity of the CAST were modest: 32% sensitivity (8/25 cases of Strep A or C were correctly identified) and 55.9% specificity (228/408 of patients negative for Strep A or C were correctly identified). The misclassification rate (measured as clear errors in prediction) was 17.1%. A lack of diagnosis (using the CAST category "uncertain") was 28.4%. The results did show that higher categories of the CAST ("likely" and "very likely") were associated with higher probability of Strep A or C infection (*P*=0.0003). Overall, 25 patients were identified as positive for Strep A or C infection by throat cultures, and of these, only 8 were identified as likely or very likely to have Strep infection using the CAST. In total, 79 patients were identified as likely or very likely to have
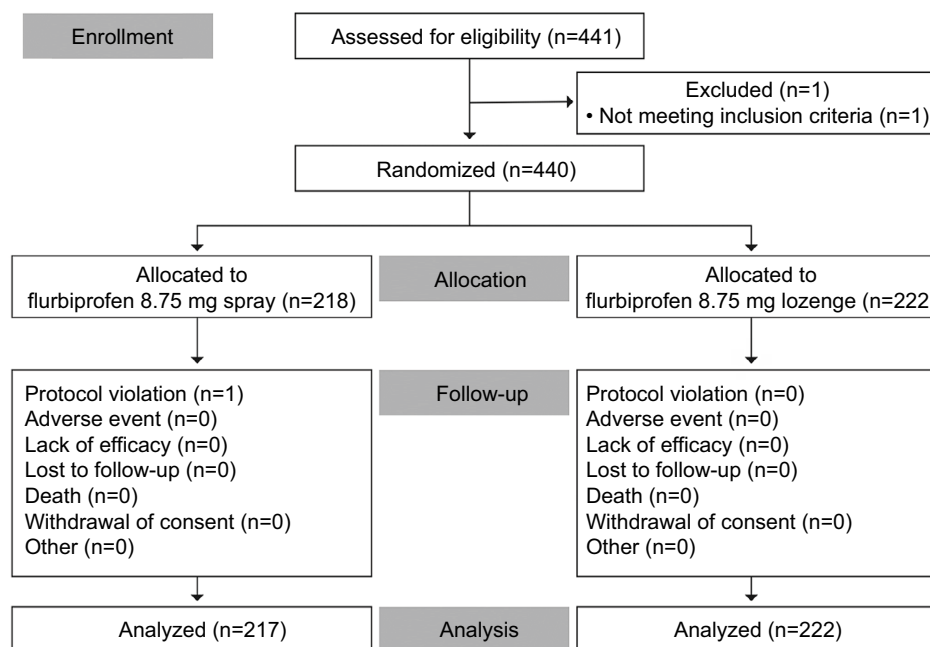

Figure 1 Patient disposition.

Table 2 Patient demographics and baseline characteristics (FAS, N=439)

	Flurbiprofen 8.75 mg spray	Flurbiprofen 8.75 mg lozenge	Total
	n=217	n=222	n=439
Age (years)			
Mean (SD)	41.6 (14.5)	42.1 (14.8)	41.9 (14.6)
Min., Max.	18, 75	18, 75	18, 75
Sex			
Male, n (%)	85 (39.2)	95 (42.8)	180 (41.0)
Female, n (%)	132 (60.8)	127 (57.2)	259 (59.0)
DSS			
Mean (SD)	69.3 (13.01)	70.9 (11.27)	70.1 (12.18)
Min., Max.	6, 100	51, 100	6, 100
SwoTS			
Mean (SD)	59.7 (17.08)	60.6 (15.49)	60.2 (16.28)
Min., Max.	8, 100	34, 100	8, 100

Abbreviations: DSS, Difficulty Swallowing Scale; FAS, full analysis set; SwoTS, Swollen Throat Scale.

Table 3 Baseline symptoms reported on URTI questionnaire (FAS, N=439)

	Flurbiprofen 8.75 mg spray	Flurbiprofen 8.75 mg lozenge	Total
	n=217	n=222	n=439
URTI-related symptom, n (%)[a]			
Coughing	26 (12.0)	26 (11.7)	52 (11.8)
Post-nasal drip	27 (12.4)	32 (14.4)	59 (13.4)
Sore throat	212 (97.7)	217 (97.7)	429 (97.7)
Swollen neck glands	41 (18.9)	46 (20.7)	87 (19.8)
Tender neck glands	74 (34.1)	73 (32.9)	147 (33.5)
Throat tickle	74 (34.1)	74 (33.3)	148 (33.7)
Throat clearing	151 (69.6)	158 (71.2)	309 (70.4)

Note: [a]Symptoms observed in >10% of patients at baseline.
Abbreviations: FAS, full analysis set; URTI, upper respiratory tract infection.

Table 4 Baseline QuaSTI score (FAS, N=439)

	Flurbiprofen 8.75 mg spray	Flurbiprofen 8.75 mg lozenge	Total
	n=217	n=222	n=439
QuaSTI score, median (min., max.)			
Agonizing	5 (0, 10)	5 (0, 10)	5 (0, 10)
Burning	5 (0, 10)	5 (0, 10)	5 (0, 10)
Difficult to swallow	7 (0, 10)	7 (0, 10)	7 (0, 10)
Dry	6 (0, 10)	5 (0, 10)	6 (0, 10)
Husky/hoarse	4 (0, 10)	4 (0, 10)	4 (0, 10)
Irritated/scratchy	7 (0, 10)	6 (0, 10)	6 (0, 10)
Like a lump in the throat	5 (0, 10)	5 (0, 10)	5 (0, 10)
Raw	7 (0, 10)	7 (0, 10)	7 (0, 10)
Swollen	6 (0, 10)	6 (0, 10)	6 (0, 10)
Tight	5 (0, 10)	5 (0, 10)	5 (0, 10)

Abbreviations: FAS, full analysis set; QuaSTI, Qualities of Sore Throat Index.

Strep infection using the CAST, meaning 71 patients could potentially have received antibiotics inappropriately.

Efficacy endpoints
Sore Throat Relief Rating Scale
ST relief, as measured by the STRRS, was evident in both treatment groups (spray and lozenge) at 1 minute, 1 and 2 hours post-dose. At 1 minute post-dose, >90% of patients in both groups experienced at least "slight" relief (≥1 on the STRRS), which increased to 98% of patients by 2 hours (Figure 2A). In total, 55%–59% of patients reported "at least moderate relief", which is a well-recognized measure of a clinically meaningful effect at 1 minute post-dose, which increased to 74%–78% of patients by

2 hours (Figure 2B). There was no significant difference between the treatment groups in ST relief at 1 and 2 hours post-dose (P>0.05).

Total sum of pain relief ratings

Pain relief over 2 hours was evident in the $TOTPAR_{0-2 \text{ hours}}$: $TOTPAR_{0-2 \text{ hours}}$ was 2.55 (95% CI: 2.29, 2.81) in the flurbiprofen spray group and 2.57 (95% CI: 2.31, 2.84) in the flurbiprofen lozenge group; the LS means difference between treatments was not statistically significant (P=0.7305).

Difficulty Swallowing Scale

In both the treatment groups, scores for difficulty swallowing improved at 1 hour (DSS 1 hour) and 2 hours (DSS 2 hours) post-dose compared with baseline (Table 5). At both of these time points, the LS means difference between the two treatment groups was not significant (DSS 1 hour, P=0.2694; DSS 2 hours, P=0.7707). Similarly, for DSS $AUC_{0-2 \text{ hours}}$, there was no significant difference in LS means between the spray (−25.84 [95% CI: −29.47, −22.21]) and the lozenge (−24.86 [95% CI: −28.46, −21.25]) groups (P=0.3678).
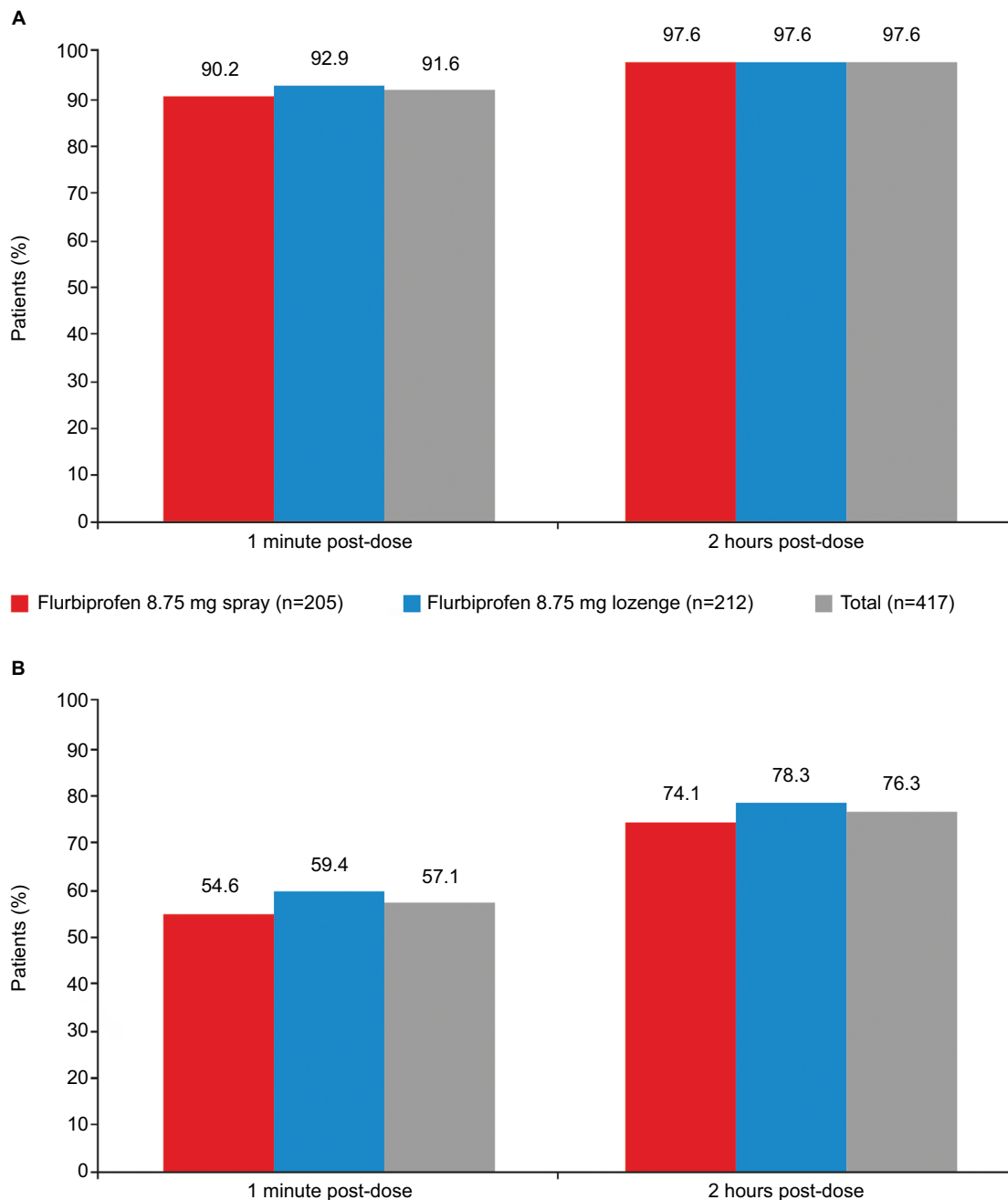
Figure 2 Patients experiencing (**A**) some relief and (**B**) at least moderate relief at 1 minute and 2 hours post-dose (PP population, N=417).
Notes: Some relief is defined as a score of ≥1 on the STRRS, that is, at least slight relief. At least moderate relief is defined as a score of ≥3 on the STRRS.
Abbreviations: PP, per-protocol; STRRS, Sore Throat Relief Rating Scale.

Swollen Throat Scale

Compared with baseline, scores for swollen throat improved at 1 hour (SwoTS 1 hour) and 2 hours (SwoTS 2 hours) post-dose in both treatment groups (Table 5). The LS means difference for change from baseline between the two treatment groups was not significant for either SwoTS 1 hour (P=0.4431) or SwoTS 2 hours (P=0.4978). There was also no significant difference in LS means between spray (−20.98 [95% CI: −24.78, −17.18]) and lozenge (−20.13 [95% CI: −23.90, −16.35]) for SwoTS AUC$_{0-2\ hours}$ (P=0.3912).

URTI questionnaire

At 2 hours post-dose, the number of patients experiencing URTI symptoms that can be attributed to or associated with ST (ST, coughing, post-nasal drip, swollen neck glands, tender neck glands, throat tickle, and throat clearing)[1,2,21–26] decreased relative to baseline (Figure 3A, B). These decreases were statistically significant for every symptom, except tender neck glands (lozenge only; P=0.0881) and throat tickle (both formulations; P=0.3113 for spray and P=0.2249 for lozenge). A small number of patients also developed ST-related URTI symptoms over the 2-hour observation period, most notably throat tickle and throat clearing (Table 6). To note, throat irritation is a commonly reported adverse event which is reported for locally delivered flurbiprofen,[12,19] and could, therefore, be the articulation of throat tickle/throat clearing seen here.

Qualities of Sore Throat Index

The mean change from baseline to 2 hours post-dose for each individual score on the QuaSTI showed significant improvements for both flurbiprofen spray and lozenge (all P<0.0001; Figure 4). The mean improvement from baseline to 2 hours

post-dose for the sum score for all items was equivalent between the two formulations (mean±SD: −29.0±16.07 [95% CI: −31.20, −26.90] for flurbiprofen spray; −27.9±16.31 [95% CI: −30.10, −25.80] for flurbiprofen lozenge; P<0.0001 from baseline for both). In addition, the mean improvement from baseline to 2 hours post-dose was equivalent between the two formulations for the three categories (sensory qualities: −20.3±11.57 [95% CI: −21.9, −18.8] for flurbiprofen spray and −19.4±11.67 [95% CI: −20.9, −17.9] for flurbiprofen lozenge; functional qualities: −5.5±3.52 [95% CI: −6, −5.1] for flurbiprofen spray and −5.4±3.65 [95% CI: −5.9, −4.9] for flurbiprofen lozenge; and the affective descriptor: −3.2±2.27 [95% CI: −3.5, −2.9] for flurbiprofen spray and −3.2±2.27 [95% CI: −3.5, −2.9] for flurbiprofen lozenge; P<0.0001 from baseline for all).

GLOBAL

At 2 hours post-dose, 81% of 217 patients in the flurbiprofen spray group and 74% of 222 patients in the flurbiprofen lozenge group assessed treatment to be either "good", "very good", or "excellent", with no significant difference between groups (P=0.4007).

Safety endpoints

Detailed safety data have been previously reported.[20] There were no significant differences between the two flurbiprofen formulations in the proportions of patients reporting treatment-emergent adverse events (TEAEs) (96/218 [44.0%] patients in the flurbiprofen spray group and 79/222 [35.6%] patients in the flurbiprofen lozenge group; P=0.0796). Of the TEAEs, most were mild and none were severe. The small number of TEAEs that were considered related to study

Table 5 Change from baseline to 1 and 2 hours post-dose in difficulty swallowing (on the DSS) and swollen throat (on the SwoTS) (PP population, N=417)

Change from baseline	Flurbiprofen 8.75 mg spray (n=205)	Flurbiprofen 8.75 mg lozenge (n=212)	Lozenge versus spray	
	LS mean (95% CI)	LS mean (95% CI)	Difference between LS means (95% CI)	*P*-value
Difficulty swallowing				
At 1 hour	−33.39 (−38.46, −28.32)	−31.69 (−36.72, −26.66)	1.70 (−1.32, 4.73)	0.27
At 2 hours	−36.53 (−42.79, −30.26)	−36.04 (−42.27, −29.81)	0.48 (−2.78, 3.75)	0.77
Swollen throat				
At 1 hour	−26.64 (−32.24, −21.03)	−25.57 (−31.14, −20.00)	1.07 (−1.66, 3.80)	0.44
At 2 hours	−30.51 (−36.21, −24.81)	−29.48 (−35.14, −23.82)	1.03 (−1.95, 4.01)	0.50

Notes: ANCOVA model: baseline (difficulty swallowing or swollen throat) + treatment + treatment sequence + center. In the ANCOVA model, the baseline DSS and SwoTS covariates were statistically significant for both the PP and FAS sets (P<0.0001).
Abbreviations: ANCOVA, analysis of covariance; DSS, Difficulty Swallowing Scale; FAS, full analysis set; LS, least squares; PP, per-protocol; SwoTS, Swollen Throat Scale.

A

B
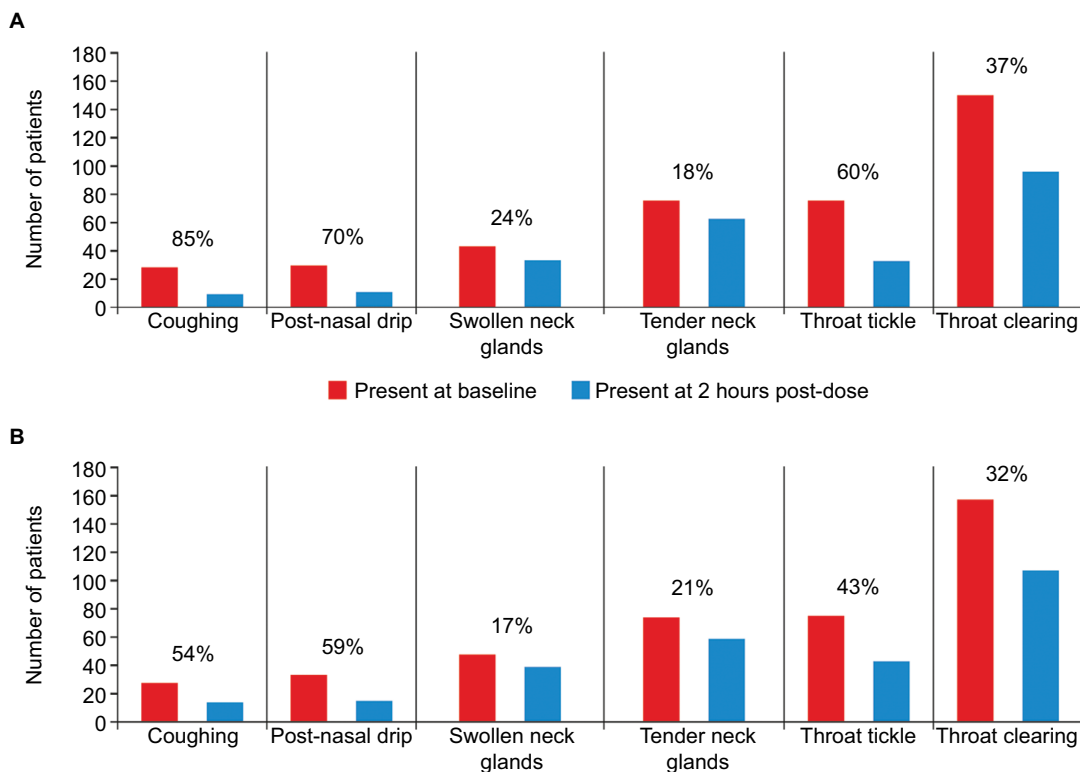
Figure 3 Symptoms of URTI at baseline and 2 hours post-dose of (**A**) flurbiprofen spray and (**B**) flurbiprofen lozenge (FAS population, N=439).

Notes: Symptoms chosen based on those associated with ST and >10% occurrence at baseline. The symptom "ST" on the URTI questionnaire was not included as this was a study entry requirement. The percentages presented in the figures are the decrease in patients with symptoms from baseline to 2 hours post-dose. Please note that, although some patients developed symptoms at 2 hours post-dose, these patients have not been included in this figure, as the cause of symptom development could not be determined (e.g., symptoms that developed at 2 hours might be new emergent symptoms, or reclassification of existing symptoms). Two patients were excluded from the analysis of cough due to missing data.

Abbreviations: FAS, full analysis set; ST, sore throat; URTI, upper respiratory tract infection.

Table 6 Patients developing URTI questionnaire symptoms related to ST over 2 hours (PP population, N=417)

Symptom	Flurbiprofen 8.75 mg spray n=205			Flurbiprofen 8.75 mg lozenge n=212		
	Present at baseline, n (%)[a]	Absent at baseline, n (%)[a]	Developed at 2 hours post-dose, n (%)[b]	Present at baseline, n (%)[a]	Absent at baseline, n (%)[a]	Developed at 2 hours post-dose, n (%)[b,c]
Coughing	24 (11.7)	181 (88.3)	2 (1.1)	23 (10.8)	189 (89.2)	3 (1.6)
Post-nasal drip	27 (13.2)	178 (86.8)	3 (1.7)	31 (14.6)	181 (85.4)	1 (0.6)
Swollen neck glands	40 (19.5)	165 (80.5)	1 (0.6)	45 (21.2)	167 (78.8)	0 (0)
Tender neck glands	73 (35.6)	132 (64.4)	3 (2.3)	72 (34.0)	140 (66.0)	5 (3.6)
Throat tickle	67 (32.7)	138 (67.3)	35 (25.4)	68 (32.1)	144 (67.9)	23 (16.0)
Throat clearing	141 (68.8)	64 (31.2)	24 (37.5)	148 (69.8)	64 (30.2)	17 (26.6)

Notes: [a]Proportion of treatment group. [b]Proportion of patients without symptoms at baseline. [c]In the flurbiprofen lozenge group, three patients (1.4%) developed ST at 2 hours post-dose.

**Abbreviations:** PP, per-protocol; ST, sore throat; URTI, upper respiratory tract infection.

treatment (11 events in nine patients for flurbiprofen spray; 6 events in four patients for flurbiprofen lozenge) were mild and as expected for flurbiprofen.

Discussion

ST may be associated with a wide variety of descriptors that reflect the different qualities of ST pain, including burn-ing, rawness, dryness, irritation/scratchiness, tightness, the sensation of having a lump in the throat, swollenness, diffi-culty swallowing, a husky/hoarse voice, and agonizing pain.[4,5] The findings of this randomized study show that flurbiprofen 8.75 mg spray and flurbiprofen 8.75 mg lozenge provide effective and equivalent relief not only from ST pain, but also from many of the other commonly reported qualities of ST.
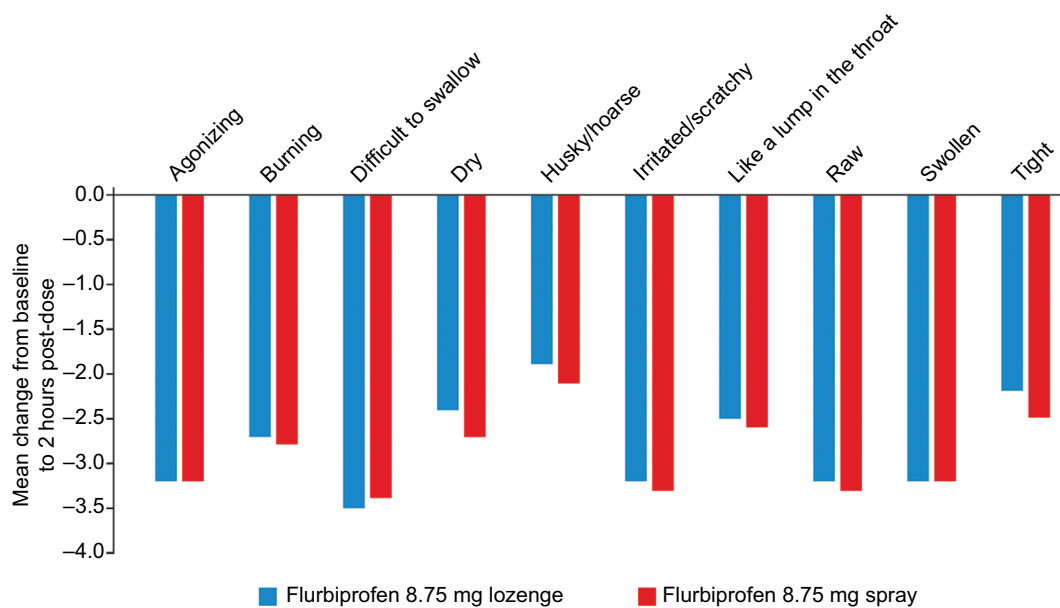
Figure 4 Mean change from baseline in QuaSTI symptoms at 2 hours post-dose.
Notes: Flurbiprofen 8.75 mg lozenge: n=221 for agonizing, difficult to swallow, raw, swollen, and tight (n=222 for all other endpoints). Flurbiprofen 8.75 mg spray: n=217 for all endpoints.
Abbreviation: QuaSTI, Qualities of Sore Throat Index.

ST relief, as measured by the STRRS, was rapid: more than half of the patients in both the spray and lozenge groups reported at least "moderate" relief from ST pain (which equates to clinically meaningful relief) at 1 minute post-completion of the two dose forms, and this proportion increased to >80% by 1 hour. The two flurbiprofen formulations also provided equivalent improvements in two common patient-reported qualities of ST, namely, swollen throat (as measured by the SwoTS) and difficulty in swallowing (an indicator of throat function measured by the DSS), over 2 hours. Significant and similar improvements from baseline to 2 hours were observed with both formulations for each of the 10 individual qualities and descriptors on the QuaSTI, the sum score for all QuaSTI items, and the three QuaSTI categories.

Responses to the URTI questionnaire at 2 hours post-dose showed a decrease in the number of patients experiencing ST-related symptoms relative to baseline; with the exception of tender neck glands in the lozenge group and throat tickle in both the spray and lozenge groups, these reductions were statistically significant. In some patients treated with flurbiprofen spray or lozenge, there was an improvement in some general symptoms of URTI during the study, which likely reflects the nature of the URTI rather than a treatment-specific effect. It must be noted, however, that some patients developed ST-related URTI symptoms at 2 hours relative to baseline. While the proportion of patients developing such symptoms at 2 hours was very small in most cases, a sizable proportion of patients in both groups developed throat tickle. It is not possible to determine whether symptoms that developed at 2 hours were genuinely new symptoms or reclassifications of existing symptoms: in the case of a throat tickle that developed at 2 hours, for example, it is possible that a more severe symptom (e.g., ST) improved by treatment with flurbiprofen and therefore reported as the less-intense "throat tickle" at 2 hours. Alternatively, throat irritation is a commonly reported adverse event for locally delivered flurbiprofen,[12,19] and could therefore be the articulation of throat tickle seen here.

Only a minority of patients in this study had a definitive diagnosis of Strep A or C infection, as confirmed by throat swab culture results (6.5% and 4.3% of patients from the flurbiprofen spray and lozenge groups, respectively). By comparison, the results of the CAST show that physicians often overestimated the incidence of Strep, with 18.0% of patients across both treatment groups considered "likely" or "very likely" to have Strep infection and would likely have been prescribed antibiotics inappropriately. Overall, the sensitivity and specificity of the CAST were modest. Therefore, these findings highlight the difficulty of accurately diagnosing Strep A infection on the basis of clinical features alone.[9] Furthermore, the throat swab results from the current study confirm that most patients would not have benefitted from antibiotics, and that effective topical medications are a more appropriate choice for the large majority of patients with acute ST due to URTI (those patients with more severe symptoms were ineligible for inclusion in the study). The

results of the current and previous studies[9] demonstrate that flurbiprofen 8.75 mg is an effective therapeutic option for rapid and long-lasting ST relief in patients both with and without Strep A or C infection and can be added to antibiotics when they are indicated to provide symptomatic relief.[9,27]

The results are aligned with previous findings for the flurbiprofen lozenge[5] and confirm that efficacy in terms of the qualities of ST is also observed for the flurbiprofen spray. The data also further support the effects of flurbiprofen 8.75 mg lozenge[28] and spray against coughing associated with ST. The equivalence demonstrated between the lozenge and spray formats means patients and health care providers can select the most appropriate format of flurbiprofen 8.75 mg without compromising the efficacy or safety.

This was a robust and well-designed study that used a number of established and validated methods, as well as a more recently developed QuaSTI, to investigate patient-reported outcomes for various qualities and symptoms of ST.[5,29–31] As the study medications had different formulations, a double-dummy technique was used to support blinding and ensure that there was no bias toward either formulation. One limitation of the study is the lack of a placebo control group. Patients were also recruited from diverse sources (general practitioners, community pharmacies, advertising) and may have presented with a wide variety of symptoms; however, the diversity of the patient population is representative of the general population seeking treatment in primary care settings. Another study limitation is that the efficacy of flurbiprofen was only assessed over 2 hours, despite previous studies showing a 6-hour duration of effect for both spray and lozenge formulations.[12,19] Additionally, the evaluation of URTI symptoms in this study could be a limitation as it only considers the presence/absence of symptoms at a single post-dose time point, rather than evaluating decreases over time using a traditional rating scale. Despite these limitations, however, the current study adds to a growing body of evidence supporting the use of flurbiprofen 8.75 mg spray or lozenge for the relief of ST caused by acute URTI.

Conclusion

Non-inferiority of the spray versus the lozenge formulation was established.[20] Flurbiprofen 8.75 mg delivered as a spray or lozenge provides rapid, effective relief from the many articulations of the broad term "ST", including a range of ST qualities that patients use to describe how their ST feels, and a number of symptoms associated with ST and broader URTI, over 2 hours. Improvements in throat function were also observed.

Disclosure

Valeria Bychkova and Adrian Shephard are employees of Reckitt Benckiser. The authors report no other conflicts of interest in this work.

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