Guaifenesin and pseudoephedrine in an extended-release bi-layer tablet as first-line symptomatic therapy in patients with acute upper respiratory tract infections (URI): A randomized, double-blind, placebo-controlled, multicenter, parallel-group study

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BACKGROUND

- Acute upper respiratory tract infections (URI) are typically caused by viruses that are not treatable with antibiotics. However, many health care providers (HCPs) are asked for, and often prescribe, an antibiotic to treat these conditions; approximately 70% of patients diagnosed with bronchitis and >90% of those with sinusitis are prescribed an antibiotic[1–3]
- The US Centers for Disease Control and Prevention (CDC) has initiated a campaign 'Get Smart about Antibiotics', to educate the public on appropriate antibiotic use and promote the development of new treatment regimens and prescribing habits[4]
- Addressing patient concerns and recommending symptom-relieving products may be as important to patient satisfaction as an antibiotic prescription for URI
- Mucinex® D (1200 mg guaifenesin + 120 mg pseudoephedrine HCl in an extended-release bi-layer tablet formulation [ER G+PSE]) is a combination of an expectorant and a nasal decongestant used to provide relief from the symptoms of URI[5]
- Previously, ER G+PSE, when used in combination with antibiotic therapy in patients with URI, was shown to shorten time to relief and improve respiratory symptoms compared with placebo[6]

STUDY OBJECTIVES

- To characterize the safety and efficacy of ER G+PSE in providing symptom relief when administered for an acute URI
- To compare ER G+PSE and placebo in the reduction of signs and symptoms associated with URI
- To determine if treatment with ER G+PSE reduces use of antibiotics in the treatment of URI when compared with placebo
- To determine if treatment with ER G+PSE reduces a patient's desire for further treatment (e.g. antibiotics)

METHODS

Study design and treatment

- This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study
- Approval for the study was obtained from the IRB (Chesapeake Research Review, Inc, Columbia, MD) and written informed consent was obtained from all patients
- Patients were randomized to ER G+PSE or matching placebo; patients took one tablet every morning and one tablet every evening with a full glass of water for seven consecutive days, in accordance with the investigational product labeling

Participants

- Eligible patients were aged 18–75 years, who presented at the HCPs clinic seeking treatment for symptoms indicative of an acute URI (e.g. common cold, acute bronchitis, acute sinusitis), with onset of symptoms within the last five days (there was no advertising for patient recruitment)
- Patients were required to have a total respiratory symptom score ≥12
- To participate patients must have met the physician's normal criteria for antibiotic therapy and be considered suitable for a 'wait and see' approach (withholding of antibiotic for ≥48 hours)

Assessments

- Patients recorded symptom ratings via an Interactive Voice Response System (IVRS) twice daily, at approximately the time of dosing, starting with the first dose
  - Patients scored the severity of seven symptoms they had experienced over the previous 12 hours (chest congestion, thickened mucus, nasal congestion, runny nose, sinus headache, sinus pressure, post-nasal drip)
  - Scoring was on a 0–5 scale where: 0=None, 1=Very mild, 2=Mild or slight, 3=Moderate, 4=Severe and 5=As bad as it could be
  - Baseline symptoms were recorded via IVRS during the Day 1 clinic visit
- Patients returned to the HCP for assessments and examinations on Day 4 and Day 8 (study end). Patients were asked:
  - If they felt the study medication alleviated their symptoms sufficiently (Day 4) and if they considered their study medication was effective (Day 8); answered on a 0–4 scale where 0=Not effective at all, 1=Somewhat effective, 2=Moderately effective, 3=Very effective, 4=Extremely effective
  - If they desired additional treatment
  - Requests for treatment were noted but the decision for treatment was made by the HCP based on their standard practice
- Other assessments, to evaluate quality of life and capture patient evaluations of treatment, were also conducted and will be reported elsewhere
- Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 12.0) terminology and classified by the investigator as mild, moderate or severe and definitely, probably, possibly, unlikely or not related to study medication

Study endpoints

- Primary efficacy endpoint: proportion of patients experiencing overall relief (defined as no symptom scores worse than 2=Mild or slight) at Day 4, evening, based on the IVRS daily diary data
- Other endpoints included: time from baseline to initial overall relief (i.e. first diary time point at which no symptom was scored worse than '2=Mild or slight'), time from baseline to sustained overall relief (i.e. overall relief maintained for at least 24 hours), total symptom score at each time point, individual symptom scores at each time point, time from baseline to treatment failure (i.e. prescribing of an antibiotic), proportion of patients not requiring an antibiotic (i.e. patients who did not receive an antibiotic prescription), patient's overall rating of the efficacy of treatment in relieving symptoms, safety
- Efficacy data are presented for the modified intent-to-treat (MITT) population (all randomized patients who received at least one dose of study medication and had ≥1 post-baseline efficacy measure)

RESULTS

Study population

- 1189 patients were enrolled at 45 sites in the USA; 1179 patients were included in the MITT population (ER G+PSE, n=591; placebo, n=588)
- Treatment groups were balanced with respect to patient baseline characteristics (Table 1)

Efficacy

Reduction of symptoms

- The number of patients experiencing overall relief at Day 4, evening, was 197 (33.3%) in the ER G+PSE group and 187 (31.8%) in the placebo group, which was not statistically significantly different (odds ratio, 0.9 [95% CI, 0.6 to 1.2]; p=0.441)

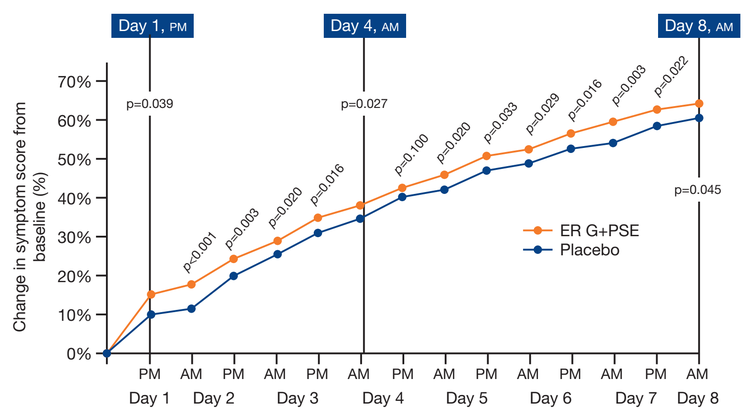
Table 1. Patient baseline characteristics (MITT population)

	ER G+PSE (n=591)	Placebo (n=588)
Mean age ± sd, years	37.4 ± 13.7	38.8 ± 13.7
Race, n (%)		
White	494 (83.6)	485 (82.5)
Black/African American	59 (10.0)	63 (10.7)
Other	38 (6.4)	40 (6.8)
Female, n (%)	395 (66.8)	404 (68.7)
Diagnosis, n (%)		
Acute bronchitis	66 (11.2)	68 (11.6)
Acute sinusitis	145 (24.5)	151 (25.7)
Rhinitis	62 (10.5)	67 (11.4)
Nasal congestion	87 (14.7)	70 (11.9)
Chest congestion	22 (3.7)	24 (4.1)
Other	209 (35.4)	208 (35.4)
Baseline total symptom score, mean ± sd	23.45 ± 4.89	23.62 ± 4.51

sd, standard deviation; MITT, modified intent-to-treat.

- There was a statistically significant improvement in time from baseline to initial overall relief with ER G+PSE over placebo (p=0.005); time from baseline to sustained overall relief also favored ER G+PSE but the difference did not reach statistical significance (p=0.072)
- A statistically significant reduction in symptoms associated with URI, assessed by IVRS diary answers by total symptom score, was seen with ER G+PSE over placebo (p=0.006)
- This statistically significant reduction in symptoms was observed for ER G+PSE vs. placebo from Day 1 (p=0.039) (Figure 1):
  - The largest difference was seen on the morning of Day 2 (p<0.001)
  - The statistically significant difference in favor of ER G+PSE remained throughout the course of the study until Day 8 (p=0.045), with the exception of the evening of Day 4 (p=0.100; primary endpoint)
- Statistically significant differences in mean change from baseline in symptom scores were observed with ER G+PSE for thickened mucus, nasal congestion, runny nose, sinus headache, sinus pressure, post-nasal drip (all p<0.05) but not for chest congestion

Figure 1. Time point comparison of change from baseline in total symptom score (MITT population)



Baseline score for ER G+PSE was 22.64. Baseline score for placebo was 22.81.
Office visits occurred on Day 1, PM, Day 4, AM and Day 8, AM.

Antibiotic sparing

- Approximately 80% of patients, regardless of treatment group, did not receive antibiotics (Table 2)
- At Day 8, antibiotics were desired by significantly fewer patients receiving ER G+PSE than patients receiving placebo (p=0.008)

Table 2. Comparison of antibiotic use, time to treatment failure, and patient desire for antibiotics in ER G+PSE and placebo groups (MITT population)

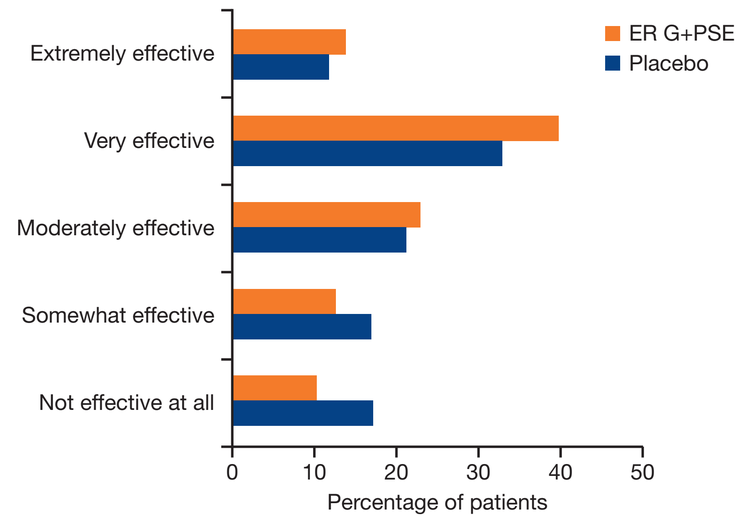
	ER G+PSE (n=591)	Placebo (n=588)
Patients <u>not</u> requiring an antibiotic, n (%)	478 (80.9)	453 (77.0)
Mean time to treatment failure ± sd, days	3.9 ± 2.02	4.1 ± 2.15
Patients desiring an antibiotic, n (%)		
Day 4	56 (9.8)[a]	68 (12.0)[b]
Day 8	24 (4.2)[b]	46 (8.0)[c]

sd, standard deviation; MITT, modified intent-to-treat.
[a]n=569; [b]n=568; [c]n=575

Treatment assessments

- Significantly more patients receiving ER G+PSE compared with placebo felt their study medication alleviated their symptoms sufficiently (p=0.048) at the Day 4 assessment
- In response to the question 'Was the study medication effective?' at the Day 8 assessment, there was a statistically significant difference overall in favor of ER G+PSE compared with placebo (p=0.025) (Figure 2)

Figure 2. Patients' end of treatment (Day 8) assessment of study medication (MITT population)



Safety

- Table 3 summarizes treatment-related AEs occurring in ≥1% of patients in either treatment group
- No serious AEs were reported during the study
- In the ER G+PSE group, eight patients (1.3%) discontinued the study due to an AE compared with five patients (0.8%) in the placebo group

Table 3. Summary of treatment-related AEs (all causalities), by system organ class and preferred term, occurring in ≥1% of patients in either treatment group (Safety population*)

	ER G+PSE (n=593)	Placebo (n=591)
Total no. of treatment-related AEs	70	32
Total no. of patients with treatment-related AEs, n (%)	58 (9.8)	28 (4.7)
Insomnia	17 (2.9)	1 (0.2)
Nervousness	7 (1.2)	4 (0.7)
Headache	7 (1.2)	14 (2.4)
Dizziness	6 (1.0)	2 (0.3)

* all patients who received at least one dose of study medication

SUMMARY

- Assessment of IVRS diary answers by total symptom score, found ER G+PSE produced a statistically significant reduction in symptoms associated with URI compared with placebo; this difference was observed both morning and evening from Day 1 to Day 8, with the exception of the evening of Day 4
- With the 'wait and see' approach and the use of ER G+PSE for symptomatic treatment, approximately 80% of patients did not receive an antibiotic, regardless of treatment group
- Compared with placebo, fewer patients in the ER G+PSE group were prescribed antibiotics and significantly fewer patients receiving ER G+PSE desired antibiotics at Day 8
  - This is most likely due to the observed improvement in symptoms
- Significantly more patients receiving ER G+PSE than placebo felt their study medication sufficiently alleviated their symptoms and was an effective treatment for their URI
- The number of patients experiencing overall relief on the evening of Day 4 (primary endpoint) did not differ significantly between the ER G+PSE and placebo treatment groups
- ER G+PSE was well tolerated by patients with URI

CONCLUSIONS

- **The combination of 1200 mg guaifenesin and 120 mg pseudoephedrine HCl in an extended-release bi-layer tablet formulation (ER G+PSE; Mucinex® D) offers a well-tolerated first-line symptomatic treatment that physicians can offer to patients instead of an antibiotic prescription for URI. A 'wait and see' approach using a symptom-relieving product (such as ER G+PSE) may reduce patient's desire for antibiotics and offer an alternative treatment, without compromising patient satisfaction**

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