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Research Article

Prospective, Non-Interventional,Multicentre study With Neo-Angin® Benzydamine, 3 Mg Lozenges For Treatment Of Acute Sore Throat, Lemon Flavour, To Evaluate The Tolerability, Acceptance And Course Of Symptoms In The Treatment Of Acute Sore Throat In Adult Patients

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ABSTRACT

Objective: To evaluate the tolerability, acceptance and course of symptoms in the treatment of acute sore throat with neo-angin® benzydamine, 3 mg lozenges for treatment of acute sore throat, lemon flavour, (neo-angin® benzydamine) in adult patients in routine clinical practice in Germany.

Rationale and background: neo-angin® benzydamine is indicated for the symptomatic local treatment of acute sore throat in adults and children over 6 years of age. The active ingredient is benzydamine hydrochloride (3 mg/lozenge). An important safety issue in self-medication is the usage according to the designated indication and dosage. Prospective observational studies provide real world evidence of safety and effectiveness of marketed drugs and contribute to the knowledge of the drug use in self-medication.

Patients and methods: Patients with acute sore throat who were prescribed neo-angin® benzydamine in the usual manner in accordance with the terms of the marketing authorization were included in the non-interventional study (NIS). Data was gathered, among others, directly from the patients using a standardized questionnaire. For evaluation, all patients with at least one documented application of the study drug and any post-baseline safety data were included in the safety evaluation set (SES) which was used for all analyses (patient satisfaction, effectiveness, tolerability). Primary study objective was patient satisfaction with neo-angin® benzydamine on the last study day. Secondary endpoints included assessment of effectiveness and tolerability of the study drug.

Results: Overall treatment satisfaction rate was 83.8% (primary endpoint) and 82.3% of patients were willing to use neo-angin® benzydamine 3 mg lozenges again**.** Time to initial relief from throat pain during administration of the first lozenge was within 5 minutes. Mean throat pain intensity score assessed on an 11-point numeric rating scale (NRS) continuously decreased during the observation period. The changes from baseline in mean NRS score over time were statistically highly significant ($p<0.0001$). The median time to obvious improvement of throat pain (i.e. 50% reduction from baseline NRS score) was 3 days. Overall, 58.8% of the patients achieved complete analgesia. Efficacy of the study drug was rated as excellent/good in 83.2% of patients, and tolerability as excellent/good in 97.0%.

Of the 456 patients included in the SES, 20 patients (4.4%) reported a total of 30 AEs, which were either mild or moderate in intensity. The physicians considered 11/30 AEs related to treatment with the study drug (adverse drug reactions, ADR). No severe or serious AES/ADRs were reported. All ADRs resolved within the 6-day observation period.

Conclusion: Short-term treatment with neo-angin® benzydamine (3 mg lozenges) was safe and very well tolerated, rapidly and significantly relieved acute throat pain in outpatients, and was associated with high patient satisfaction. No serious AEs or ADRs were reported. The study results confirm the positive risk-benefit profile of benzydamine hydrochloride lozenges.

Keywords: Benzydamine hydrochloride lozenges; Acute sore throat; Non-interventional study (NIS)

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INTRODUCTION

Adults suffer in average two to four and children six to eight upper respiratory tract infections per year usually during the colder months of the year [1]. One of the most common symptoms is acute sore throat due to an inflammatory reaction caused by a viral infection, mostly by rhinoviruses and coronaviruses, which comprise more than 25% of viral infections of the upper respiratory tract [2–4]. In addition to viral pathogens, there are also certain bacteria, which cause pharyngeal infections. These include Streptococcus pyogenes (group A beta-haemolytic streptococcus), groups C or G beta-haemolytic streptococci, Mycoplasma pneumonia, and Chlamydia pneumoniae [1]. The onset of pharyngitis symptoms is usually sudden. Duration of sore throat is in average 3.5 to 5 days. Spontaneous remission of pharyngeal symptoms occurs with a high frequency, and 80–90% of patients are free of symptoms after one week [4].

Treatment depends on the cause of pharyngitis. Viral pharyngitis is generally treated symptomatically with appropriate oral pain relievers [5]. Other supportive therapies like home remedies and local treatments are applied as well. However, antibiotic treatment should be initiated if GAS (Group A Streptococcus) pharyngitis is present [3, 4, 6].

Background and rationale

neo-angin® benzydamine for acute sore throat lemon flavour (hereafter referred to as neo-angin® benzydamine) is a medicinal product indicated for the symptomatic local treatment of acute sore throat in adults and children (over 6 years of age) [7]. The active ingredient of neo-angin® benzydamine is benzydamine hydrochloride, a locally acting non-steroidal anti-inflammatory drug (NSAID). Due to its local anaesthetic and analgesic characteristics, benzydamine hydrochloride provides a reasonable analgesic and anti-inflammatory treatment for acute sore throat [8]. According to the current Summary of Product Characteristics (SmPC) [7], the most common adverse events (AE) reported for benzydamine hydrochlorides are hypersensitivity reactions, anaphylaxia, and oral hypoaesthesia. Other, rarely occurring AE are photosensitivity, burning sensation in the mouth or dry mouth [7].

An important safety issue in self-medication is the usage according to the designated indication and dosage. Prospective observational studies provide real world data regarding safety and effectiveness of marketed drugs and contribute to the knowledge of the drug use in self-medication.

OBJECTIVES

The aim of this non-interventional study (NIS) was to evaluate the tolerability, acceptance and course of symptoms in patients treated with neo-angin® benzydamine in adult patients in routine clinical practice in Germany. The primary objective was to assess patient satisfaction with neo-angin® benzydamine on the last study day Day 4 (Day 5 or Day 6 at the latest). Secondary objectives included the evaluation of the effectiveness of the study drug on the symptoms of acute sore throat and the tolerability of the treatment.

STUDY DESIGN

The study was designed as a national, multicentre, prospective, uncontrolled, single group observational study in accordance with the German Medicinal Products Act (Arzneimittelgesetz, AMG). The study was carried out in accordance with the recommendations for planning, conducting and analysing of observational studies published in 2010 [9] by the German Federal Institute for Drugs and Medical Devices (BfArM) together with the Paul-Ehrlich-Institute (PEI), and the recommendations for quality assurance in NIS published in 2014 [10] by the German Association of Research-Based Pharmaceutical Companies (VFA) . The study is registered in the BfArM's public NIS database (No 7181) [11].

The prospective cohort design was chosen to generate further data about effectiveness and tolerability of neo-angin® benzydamine in adult patients.

The study drug was prescribed in accordance with the terms of marketing authorization. The prescription was explicitly separated from the decision to include the patient in the study. The data was gathered directly from the patients using a standardized questionnaire. No additional diagnostic procedures were applied, and epidemiological methods were used for the analysis of collected data.

The study was performed in Germany during January 2018 to April 2018. Primary care physicians (family doctors, general practitioners) and secondary care physicians (internists, Ear, Nose and Throat [ENT] specialists) who are familiar with the symptoms and treatment of acute sore throat were invited to participate in the study.

Patients could participate in this observational study if they met all of the following criteria: at least 18 years old, acute sore throat (acute pharyngitis), treatment with neo-angin® benzydamine prescribed according to the physician's decision, no contraindications according to SmPC [7], written informed consent. The diagnosis "acute sore throat" was based on the experiences of everyday clinical practice. Concomitant medications and diseases were not specified.

Study medication

neo-angin® benzydamine is indicated for symptomatic local treatment of acute sore throat in adults and children who are at least 6 years old. Physician's judgment to treat the patient with benzydamine lozenges followed common practice of drug prescription within the marketing authorisation and was explicitly separated from the decision to include the patient in this study.

The observation period for the individual patient was 4 days (maximum 6 days). Patients who had agreed to data collection when visiting the physician for acute sore throat (Visit 1/Day 1) were asked to participate in the follow-up assessment, scheduled 3 days (maximum 5 days) after Visit 1. The follow-up (FU) assessment was done during an optional second site visit or via phone (FU-visit/FU phone call=optional visit 2 to evaluate the patient's health) based on patient decision.

Study-specific patient data were collected using an electronic case report form (eCRF), and a patient questionnaire in paper form (diary). For demographic assessment, age (years) and gender (male/female) were recorded in the eCRF at Visit 1. Patient's initial rating of throat pain intensity (baseline throat pain documented in the questionnaire in the doctor's office) was checked by the physician at visit 1 to ensure that the patient's pain intensity score was ≥1 on the 11-point numeric rating scale before the start of neo-angin® benzydamine. Patient's baseline throat pain intensity score was documented in the patient questionnaire on Day 1.

The adherence to recommended standard dose of 3 lozenges per day (according to SmPC) was calculated based on the drug accountability data documented in the eCRF. 6/456 patients did not record the number of lozenges taken per day in the questionnaire (missing data).

Patients were asked to record the intensity of throat pain in the questionnaire at the physician's office before administration of the first lozenge (baseline, morning of Day 1) and in the evening of the same day (Day 1), and twice-daily (morning and evening) on Days 2-4 (Day 5 or Day 6 at the latest) using an 11-point numeric rating scale (NRS). Every morning (Days 1–6), during administration of the first lozenge time to initial relief from pain was documented (<1 min, 1–2 min, 2–3 min, 3–5 min, 5–7 min, 7–10 min, >15 min). Any disease or symptom newly occurring during the study or a worsening of a pre-existing disorder was recorded as an AE.

Statistics

All patients with at least one documented application of the study medication and any post-baseline safety data were included in the safety evaluation set (SES) which was used for all analyses (patient satisfaction, effectiveness, tolerability). All data was listed and summary tables for continuous and categorical data as well as graphical illustrations were provided where appropriate. Summary tables for continuous data display the number of valid observations (N_{valid}), number of missing observation values (N_{miss}), arithmetic means, standard deviation (SD), minimum, median and maximum. Categorical data are displayed in tables by absolute frequencies and relative frequencies (percentages). Logistic regression was used to explore associations between independent variables, outcome and covariates (e.g. study day, centre, baseline throat pain intensity, sex, age). Incidences including confidence intervals (CI) were calculated from the model on day-level (Day 4, Day 5, Day 6), age-level and overall. For patient satisfaction and global judgments of efficacy and tolerability, the changes in percentages of patients between Day 4 and Day 5, and between Day 5 and Day 6 were evaluated using Fisher's exact test. For the course of throat pain intensity during treatment, differences in NRS rating scores between post-baseline measurements and baseline were analysed using the Wilcoxon signed rank test.

RESULTS

Patient data was collected at 29 of 30 contracted centres across Germany (14 general practitioners, 15 ENT specialists). A total of 463 patients with acute sore throat gave written informed consent to take part in this observational study. Seven patients did not return the questionnaire (diary) and were excluded from data analysis; finally, data of 456 patients were analysed (SES). Mean age was 43.8 years (SD 17.2; range: 18–90 years) with a higher percentage being female (59.0%). The median study duration was 6.0 days (range: 1–53 days). In total, 3.3% of patients (15 of 456) terminated the study early (6 patients were lost to follow-up, 5 patients experienced an adverse drug reaction [ADR], 2 patients were free of symptoms, 1 patient did not like the taste of the lozenges, 1 patient was not satisfied with the efficacy of the study drug).

Treatment duration was calculated based on the date of the last day documented by the patient in the questionnaire (diary). If the patient did not return the diary, the date of the study termination page (eCRF) completed by the physician was used for calculation. The median treatment duration was 4.0 days (range: 1–28 days). The maximum treatment duration of 28 days was recorded for six patients who did not return the diary. Excluding those six from calculation, the median treatment duration was 4.0 days (range: 1–9 days). Among the 450 patients who had valid data for the analysis of treatment compliance, 92.9% (SD 19.5%) adhered to the standard dose (range: 33–189%). The high maximum value of 189% treatment compliance is due to the fact that the duration of actual administrations of lozenges recorded by one patient (6 days x 6 tablets) was markedly longer than the study duration (4 days x 3 tablets) recorded for this patient in the eCRF.

Patient satisfaction

201/456 patients (44.1%) rated their satisfaction with treatment on Day 4, 86 (18.9%) on Day 5, 149 (32.7%) on Day 6. For 20 patients (4.4%) satisfaction data was missing. Hence, 436 of 456 patients were evaluable for the analysis of the primary endpoint and 20 patients were excluded due to missing data (N_{miss}=20).

Overall, 83.7% (N=365/436 patients) were very satisfied with the study medication on the last study day (Day 4, Day 5 or Day 6). The percentage of patients who were very satisfied with treatment was slightly higher in men (87.2%) than in women (81.3%). Satisfaction with treatment was 90.5% on Day 4 (N=182/201), 86.0% on Day 5 (N=74/86), and 73.2% on Day 6 (N=109/149) (Figure 1).

The results of a logistic regression analysis showed that the "primary day", i.e. the day of being symptom-free, significantly (*P*=0.0069) affected patients' assessments of treatment satisfaction while the covariates "baseline throat pain intensity" (*P*=0.6851), "gender" (*P*=0.1769), "median age" (*P*=0.6854), and "centre" (*P*=0.9488) had no effect on patient satisfaction with treatment. The chance of being (very) satisfied with treatment was 2.75 times higher for patients who completed the study on Day 4 compared to patients who completed the study on Day 6 (Odds Ratio [OR], 95 % confidence interval [CI] 1.46–5.17). The OR of 1.53 in the comparison of Day 4 vs. Day 6 signifies no significant association between positive satisfaction ratings if symptom-free on day 4.

Efficacy

On 5 February 2018 the Observation Plan was amendment to add a patient rating in the questionnaire on Day 1 about the initial relief from pain during administration of the first lozenge on

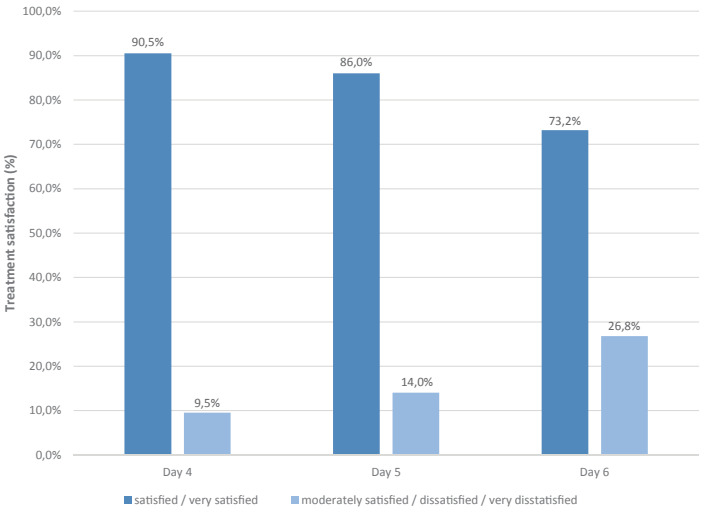

Figure 1: Treatment satisfaction: Patient ratings on the last study day (SES: N_{valid}=436).

each day. On Day 1, 50.7% of 260 patients started to feel relief from throat pain within 5 min after administration of the first lozenge, with most patients reporting initial pain relief after 3–5 min (23.1%). Among the 49.3% of 260 patients who started to feel relief from throat pain later than 5 min after administration of the first lozenge, 20.8% reported initial pain relief after 5–7 min, 8.5% after 7–10 min and the remaining 20.0% of patients after 10 to >15 min.

On Day 2, the percentage of patients who started to feel relief from throat pain within 5 min after administration of the first lozenge increased to 63.5% of 260, with initial pain relief reported most commonly after 3–5 min (25.4%) or 2–3 min (24.2%).

Within the next two days of treatment, the percentage of patients who started to feel relief from throat pain within 5 min after administration of the first lozenge further increased to 69.5% of 249 patients on Day 3, and to 72.4% of 221 patients on Day 4, with initial pain relief reported most commonly after 3–5 min (Day 3: 27.7%; Day 4: 21.3%) or 2–3 min (Day 3: 23.7%; Day 4: 22.6%). The percentage of patients who started to feel relief from throat pain within 2 min after the first lozenge increased from 8.8% of 260 on Day 1 to 28.5% of 221 on Day 4. Little can be concluded from the results for Day 5 and Day 6 because of the small number of patients available for analysis (Day 5: N=121; Day 6: N=74).

Patients with missing values were excluded from the analysis (N_{miss}=17/456, 3.7%). Until the end of the 6-day observation period, 258/439 patients (58.8%) achieved complete resolution of throat pain. The resolution rate was higher on Day 4 (69.7% of N=201) compared to Day 5 (65.2% of N=89) and Day 6 (40.3% of N=149) (Figure 2).

A logistic regression analysis was performed based on the data of 422/456 patients to determine the effect of possible confounders on the binary response variable "complete resolution of throat pain (symptom-free) until the last study day: yes/no". The results showed that "median age" (*P*=0.0446), "center" (*P*=0.0127) and "day of symptom-free" (*P* <0.0001) significantly affected the onset of complete resolution of throat pain on Days 4–6 while the covariates "baseline throat pain intensity" (*P* =0.7751) and "gender" (*P*=0.2527) had no effect.

The ORs and the 95% CI calculated separately by onset of complete

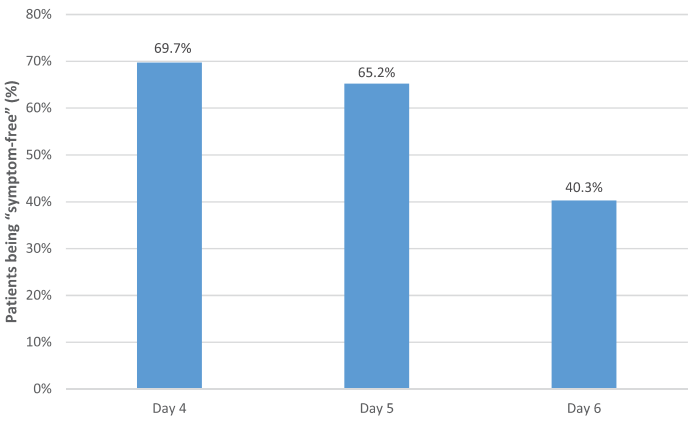

Figure 2: Percentage of patients with complete resolution of throat pain ("symptom-free") until the last study day (SES): Complete resolution of throat pain was defined as score 0 (=no pain/symptom-free) on the 11-point numeric rating scale (NRS) .

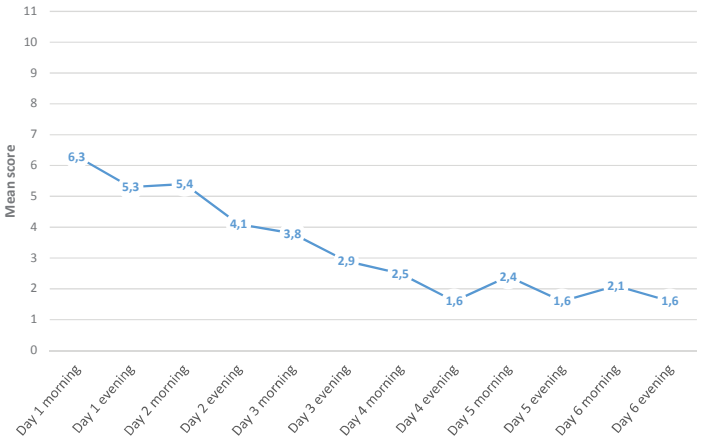

Figure 3: Mean throat pain intensity (NRS scores) over treatment period: 11-point numeric rating scale (NRS) ranging from 0 (no pain /symptom-free) to 10 (worst possible pain).

resolution (Day 4, Day 5 or Day 6), showed a significant 95% CI only for Day 6 in the comparison age < median vs. age > median (OR 0.41, 95% CI 0.20–0.84). The OR of 0.41 signifies a 0.41 likelihood of complete resolution on Day 6 for patients below the median age of 42 years.

Based on patients' ratings on the questionnaire data, the mean throat pain intensity score was 6.3 points (SD 1.9) at Visit 1 (morning of Day 1, baseline N_{valid}=449), decreased to 5.3 points (SD 2.3) until the evening of the same day (evening of Day 1, N_{valid}=449), and further decreased to 1.6 points (SD 2.2) on the evening of Day 4 (N_{valid}=439), and to 1.6 points (SD 2.1) on evening of Day 6 (N_{valid}=149) (Figure 3).

On the first day of treatment (change from baseline to day 1evening), the mean throat pain intensity decreased by 1.0 score point (SD 2.6). Thereafter, mean throat pain intensity continuously decreased with mean reductions of 2.1, 3.4, 4.7, 4.9, and 5.0 score points from baseline to the evening of Days 2, 3, 4, 5 and 6 respectively (SD values were 2.6, 2.7, 3.0, 3.2 and 3.0, respectively). The decreases from baseline in mean throat pain intensity scores showed a high statistical significance (p<0.0001) at every specified point in time (Day 1 to Day 6) (Figure 4).

Of the 456 treated patients (SES), 275 (60.3%) provided data for the analysis of "duration of effect" (i.e. relapse after complete

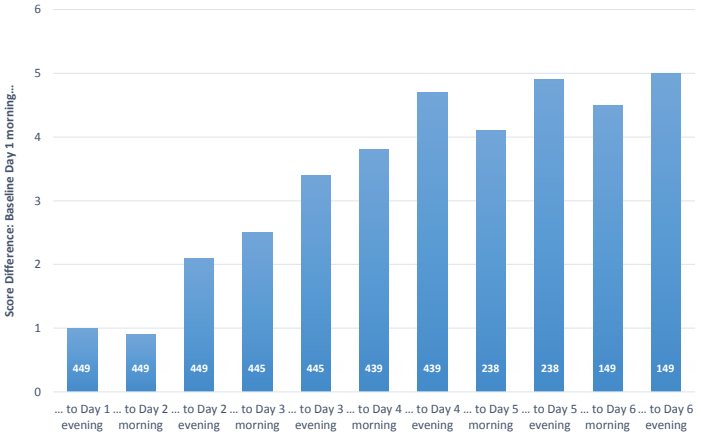

Figure 4: Change from baseline throat pain intensity (mean NRS score) up to Day 6: Mean change in the score on the 11-point scale with respect to the symptoms of throat pain during the duration of the treatment; Numbers: Number of patients per assessment.

resolution of throat pain at any point during treatment). Among these 275 patients who were pain-free at any point during treatment, 243 (88.4%) stayed symptom-free and 32 (11.6%) had a relapse during the observation period.

Based on the results of a logistic regression analysis, the covariates "baseline throat pain intensity" (*P*=0.1592), "gender" (*P*=0.4103), "median age" (*P*=0.4933), and "center" (*P*=0.3909) had no effect on the outcome variable relapse after complete resolution of throat pain.

Physicians rated the efficacy of the study drug as excellent/good in 83.2% of patients (307/369 patients). Based on the results of a logistic regression analysis, the covariates "baseline throat pain intensity" (*P*=0.2985), "gender" (*P*=0.7707), "median age" (*P*=0.2363), and "centre" (*P*=0.5685) had no effect on the physician's efficacy judgement after the follow-up assessment (Figure 5).

In total, 359 (82.3%) of 436 evaluable patients were willing to use the study drug again, 37 patients (8.5%) answered they would not use the lozenges again, and 40 patients (9.2%) were not sure whether they would use them again (Figure 6).

Tolerability

The physicians rated the tolerability of the study drug as excellent/good in 97.0% of the patients (359/370 patients) (Figure 7). Based on the results of a logistic regression analysis, the covariates "baseline throat pain intensity" (*P* =0.6209), "gender" (*P*=0.2051), "median age" (*P*=0.9851), and "centre" (*P* =0.1310) had no effect on the physician's efficacy judgement after the follow-up assessment.

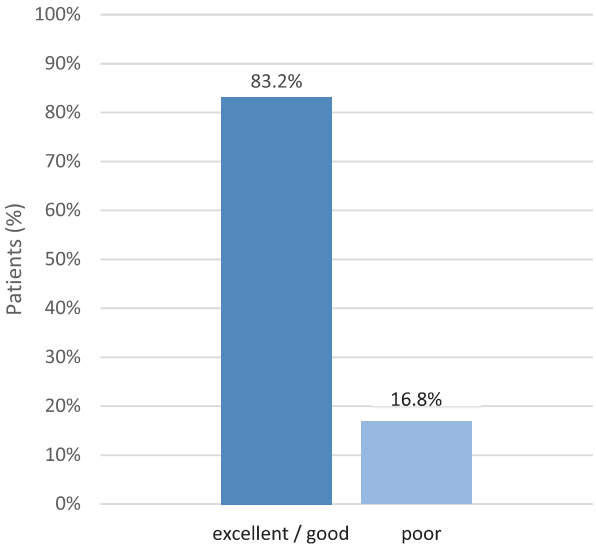

Figure 5: Physicians' global judgements of efficacy of neo-angin® benzydamine.

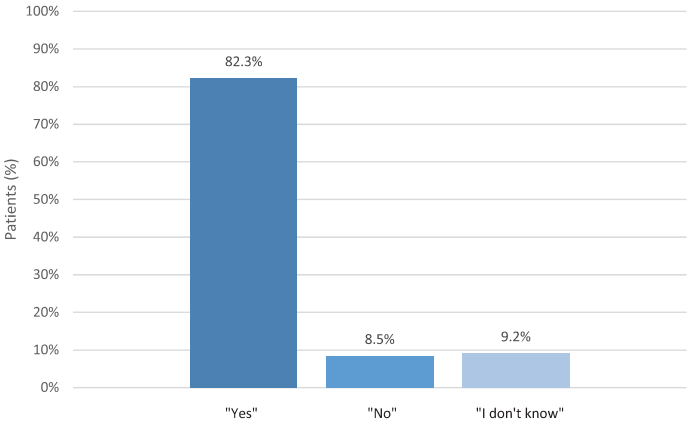

Figure 6: Patient's willingness to administer neo-angin® benzydamine again in the future for sore throat (N_{valid} = 436).

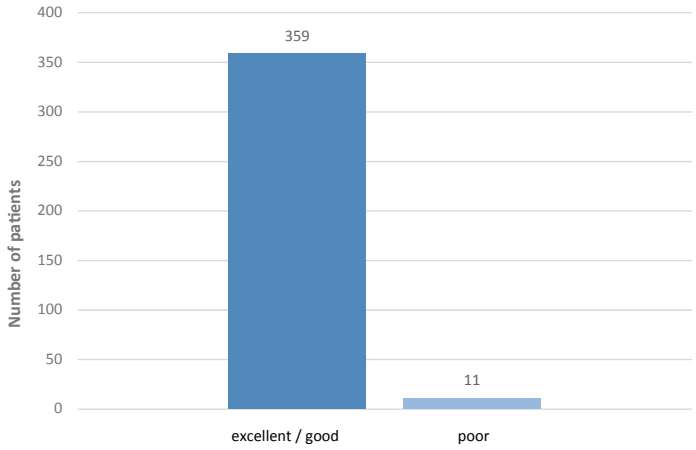

Figure 7: Physicians' global judgements of tolerability of neo-angin® benzydamine (N=370).

20/456 treated patients, 20 (4.4%) reported a total of 30 AEs, which were either mild (23/30 AEs, 76.7%) or moderate (7/30 AEs, 23.3%) in intensity. There were no severe AEs reported. The physicians considered 11/30 AEs reported for 10/456 patients (2.2%) probably, possibly, or unlikely related to treatment with the study drug (adverse drug reactions, ADR). All ADRs were considered as mild (8/11) or moderate (3/11) intensity. There were no severe or serious AES/ADRs reported. The only ADR experienced by more than 1 patient was oral hypoesthesia (2/456 patients, 0.4%). All 11 ADRs resolved within the 6-day observation period and were mild or moderate in intensity.

DISCUSSION

Except for the global efficacy and tolerability assessments by physicians, the results of this study are based on patient-reported outcome data via self-administered questionnaire. Self- report measures are a necessary tool in clinical research. Possible disadvantages of using a questionnaire (diary) include non-adherence (e.g., missing data, not keeping the schedule for data documentation), symptom recall (e.g., twice daily rating of throat pain may have increased the perception of symptom severity), and problems in using rating scales. Persons may also have different ways of filling out ratings scales. On the other hand numeric and verbal rating scales provide more nuanced responses than just yes/no [12].

To overcome certain limitations, the questionnaire (diary) included an example for using the rating scale and each patient received instructions on how to fill in the questionnaire at the physician's office (Visit 1). Patients who did not return for Visit 2 (optional follow-up visit) received a follow-up phone call and were reminded to send back the completed questionnaire. The questionnaire was intended to track the effectiveness of the study drug on the main symptom of acute sore throat (feeling of throat pain) and to collect data on patient satisfaction with treatment (primary endpoint) and adherence to the dose recommended in the SmPC over 4 days (maximum 6 days).

Treatment satisfaction is a patient reported outcome that gives a good insight into the patient's perspective on their current treatment. In this study, the day of being symptom-free, significantly

affected patients' assessments of treatment satisfaction (logistic regression analysis: *P*=0.0061; OR 0.36, 95% CI 0.19–0.68 in the Day 4 vs. Day 6 comparison). The percentage of patients with treatment satisfaction ratings of very good/good was 90.7% of 204 evaluable patients on Day 4. This is higher than the percentage of patients who achieved complete resolution of throat pain until Day 4 (69.7% of 201). It can be assumed that the rapid improvement in throat pain intensity (median of 3 days to 50% reduction from baseline NRS score) and the good tolerability of local treatment based on the physicians' ratings of global tolerability as excellent/good (97.0% of 370 evaluable patients) have contributed to the high percentage of patients who were (very) satisfied with the lozenges. This is supported by the fact that 82.3% of 436 evaluable patients were willing to administer the lozenges in the future for sore throat. The physicians assessed global efficacy of the lozenges as excellent/good for 83.2% of 369 evaluable patients.

The occurrence of side effects under 4 to 6 days treatment with the lozenges was low (10/456 patients, 2.2%, reporting a total of 11 ADRs of mild or moderate rating). No severe ADRs were reported. The majority of ADRs (9/11 events, 81.8%) were mild to moderate transient oropharyngeal complaints, most of these ADRs are expected during local treatment with benzydamine hydrochloride, the active ingredient of the lozenges. The other 2 ADRs were moderate abdominal distension and mild pruritus, each reported for 1 patient.

The statistical analysis is based on the data of 456 adult patients with acute sore throat receiving 4 days treatment with the study drug in 30 doctor's offices (study centres) across Germany. The results of this well-powered observational study provide good evidence on the patients' perspective on the tolerability, acceptance, and the course of throat pain under treatment with the lozenges in routine clinical practice in Germany.

CONCLUSION

Short-term treatment with neo-angin® benzydamine (3 mg lozenges) was safe and very well tolerated, rapidly and significantly relieved acute throat pain in outpatients, and was associated with high patient satisfaction ratings. Adherence to the recommended therapeutic dose was 93%. No serious ADRs or ADRs of severe intensity were reported. The study results confirm the positive risk-benefit profile of neo-angin® benzydamine.

AUTHOR CONTRIBUTION

All authors contributed towards data analysis, drafting and critically revising the paper, and agree to be accountable for all aspects of the work.

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DISCLOSURES

The authors have no conflict of interest. Cassella-med, Cologne, Germany is the sponsor of the study.

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