Sponsor	MEDICE Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37, 58638 Iserlohn, Germany	
Name of Finished Product	Dorithricin® Halstabletten Classic	
Name of Active Substance	Tyrothricin, Benzalkonium Chloride, Benzocaine	
Title of study	A multi-centre, randomized, placebo-controlled, double-blind, parallel-group study investigating safety and efficacy of a sore throat lozenge in the symptomatic treatment of patients with acute pharyngitis	
EudraCT number	2016-003962-24	
Principal Investigator	Dr. med. Jürgen Palm, Rückersdorferstr. 61, 90552 Röthenbach/Pegnitz	
Publication	Palm et al. Efficacy and safety of a triple active sore throat lozenge in the treatment of patients with acute pharyngitis: Results of a multi-centre, randomised, placebo-controlled, double-blind, parallel-group trial (DoriPha).Int J Clin Pract. 2018 Dec;72(12)	
Study period	First patient in: 19-01-2017	Last patient in: 02-07-2017
Phase of development	IV	
Trial objective	The primary objective of this study was to demonstrate that the effect of Dorithricin® lozenges is superior to placebo in the treatment of acute pharyngitis.	
Methods	This was a prospective, randomized, parallel-group, placebo-controlled, double-blind, multi-centre, Phase IV study. Patient data were collected by the investigator during 2 study visits using an electronic case report form (eCRF). Additionally, a paper-based diary and questionnaire were used for the patient to document symptoms, drug administration, side effects, smoking habits and to answer consumer-related questions from Visit 1 to Visit 2. *Day 0/Visit 1 (documentation in the eCRF and patient questionnaires)* The investigator performed the Tonsillo-Pharyngitis Assessment (TPA), rating 0-3 score points for each of the following signs and symptoms (depending on the presence and severity on physical examination): oral temperature, oropharyngeal color, size of tonsils, number of oropharyngeal enanthems (vesicles, petechiae, or exudates), largest size of anterior cervical lymph nodes, number of anterior cervical lymph nodes, and maximum tenderness of someanterior cervical lymph nodes. The TPA score ranges from 0 to 21; a TPA score ≥5 (inclusion criterion) indicated pharyngitis. A patient questionnaire was used for the assessment of throat pain (sore throat) and difficulty in swallowing. The patient assessed the symptoms pain intensity and difficulty in swallowing over a period of 1–2 hours (2 hours preferred): before the initial dose (t0) and 5 (±1), 10 (±1), 15 (±1), 20 (±1), 30 (±3), 45 (±3), 60 (±3), 75 (±3), 90 (±3),105 (±3) and 120 (±6) minutes after the initial dose.	

	Intensity of throat pain was assessed using an 11-point numeric rating scale (11-point NRS) with 0 representing one pain extreme (no pain) and 10 representing the other pain extreme (severe pain). The patient was instructed to evaluate the severity of throat pain at that moment. Patients had to have a baseline NRS score ≥8 at screening (inclusion criterion; changed to ≥7 points by protocol amendment no.1). Difficulty in swallowing was assessed using a visual analogue scale 100 mm in length (100-mm VAS) anchored by 2 verbal descriptors, one for each symptom extreme (0 mm = not difficult, 100 mm = very difficult). The patient was instructed to swallow and to point on the scale how difficult it was to swallow at that moment. Patients had to have a baseline VAS score ≥50 mm at screening (inclusion criterion). *Days 0 – 3 (documentation in the diary)* Patients were asked to keep a diary from Day 0 to Day 3 for monitoring of throat pain and difficulty in swallowing (Days 0-2), for recording the number of lozenges taken per day (Days 0-3), and any further symptoms or side effects, and for recording smoking habits and the number of cigarettes, if applicable (Days 0-3). Additionally (only on Day 3), the patient recorded in the diary if he/she would recommend the study drug to others and was willing to use the medication in the future. On Days 0, 1, and 2, the patient assessed throat pain (11-point NRS) and difficulty in swallowing (100-mm VAS) in the evening before the administration of the last lozenge (documentation in the diary). If the two symptoms were not present at this point in time, the patient also recorded the approximate time of last throat pain and difficulty in swallowing on this day or the day before. *Day 3/Visit 2 (documentation in the eCRF and patient questionnaire)* The investigator performed the TPA. The patient assessed his/her throat pain and difficulty in swallowing in a patient questionnaire. Both, the patient and the investigator were asked to assess the tolerability of study medication using a 5-point verbal rating scale (VRS) ('excellent', 'good', 'moderate', 'bad', and 'very bad'). The patient and the treating investigator
Number of patients	Of 328 patients screened, 321 patients were randomized and received investigational treatment. 160/321 patients (49.8%) were treated with Dorithricin® (verum) and 161/321 patients (50.2%) received placebo. Patients analysed / Dorithricin® / Placebo / Total SES 160 (100.0%) 161 (100.0%) 321 (100.0%) FAS 156 (97.5%) 160 (99.4%) 316 (98.4%) PP 140 (87.5%) 146 (90.7%) 286 (89.1%) SES = safety evaluable set; FAS = full analysis set; PP = per protocol population
Diagnostic and main inclusion criteria	• Male and female outpatients aged ≥18 years • Signed informed consent form

	• Clinically diagnosed acute pharyngitis (TPA ≥5)Recent onset of symptoms (≤24 hours) • Pain intensity of ≥8 on an 11-point NRS (changed to ≥7 points by protocol amendment no.1) • Difficulty in swallowing (100-mm VAS ≥50 mm)
Investigational substance	One lozenge contained 0.5 mg tyrothricin, 1.0 mg benzalkonium chloride, and 1.5 mg benzocaine Mode of Administration: Orally (lozenge was to be sucked slowly until it fully dissolved in the mouth) Dose: Up to 8 lozenges per day Ch.-B.: PL 6444
Control substance	Placebo (lozenges) Mode of Administration: Orally (lozenge was to be sucked slowly until it fully dissolved in the mouth) Dose: Up to 8 lozenges per day Ch.-B.: PL 6444
Duration of treatment	72 (-1/+2) hours (from Day 0 to Day 3)
Criteria for evaluation	
Efficacy	*Primary efficacy endpoint:* • Percentage of Total Responders assessed at Visit 2 (approx. 72 hours after first application of treatment). A patient was defined as Total Responder in case of a complete resolution of throat pain and difficulty in swallowing at Visit 2 (approx. 72 hours after first application of treatment). This was documented as complete disappearance of both pharyngitis symptoms, i.e. no throat pain (score=0 on the 11-point NRS scale) and no difficulties in swallowing (0 mm on the 100-mm VAS scale) based on the questionnaire completed at the study site (Visit 2). *Secondary efficacy endpoints*: • Percentage of patients with complete resolution of throat pain 48 hours p.i.d. and symptom-free until end of study (up to 72 hours p.i.d) • Difference in responder rates for single symptoms of acute pharyngitis: ○ Percentage of patients with complete resolution of throat pain 72 hours post initial dose (p.i.d.) ○ Percentage of patients with complete resolution of throat pain 48 hours p.i.d. and symptom-free until end of study (up to 72 hours p.i.d) ○ Percentage of patients with complete resolution of difficulty in swallowing 72 hours p.i.d. ○ Percentage of patients with complete resolution of difficulty in swallowing 48 hours p.i.d. and symptom-free until end of the study (up to 72 hours p.i.d) • The baseline differences for single symptoms of acute pharyngitis: ○ Baseline difference in throat pain at Visit 2 (average change in NRS score from t0 to 72 hours p.i.d.) ○ Baseline difference in difficulty to swallow at Visit 2 (average change in mmVAS from baseline t0 to 72 hours p.i.d.)

	• Time to free of both symptom(s) (throat pain and difficulty in swallowing), time to free of throat pain, and time to free of difficulty in swallowing
	• Symptom relief after administration of the initial dose:
	  ○ Intensity of symptoms analysed by mixed model for repeated measures (MMRM) using centre as random effect, treatment as fixed effect, an indicator variable which states the documented assessment at 2 hours p.i.d. and 1 hour p.i.d. as fixed effect, baseline as covariate and baseline difference in symptom intensity as dependent variable repeated in time, separately for throat pain and difficulty in swallowing
	  ○ Means of symptom intensity and their corresponding confidence intervals (CI) over time were graphically displayed by treatment group, separately for throat pain and difficulty in swallowing
	  ○ Time to symptom reduction were analysed by the Log-rank test, separately for throat pain (time to reduction by at least 1 NRS score point) and difficulty in swallowing (time to reduction by at least 10 mm on VAS)
	  ○ The sum of symptom intensity differences over 1 hour and 2 hours p.i.d. (see Section 9.7.1.1.5) were analysed by Wilcoxon Rank-sum test, separately for throat pain and difficulty in swallowing
	  ○ Percentage of patients with reduction in baseline symptom intensity by at least 50% 1 hour and 2 hours p.i.d. was analysed using GEE (analogous to primary endpoint analysis), separately for throat pain (at least 50% reduction of baseline NRS score) and difficulty in swallowing (at least 50% reduction of baseline mm VAS)
	Additional endpoints:
	• Change in the TPA score and TPA single symptom scores from Visit 1 to Visit 2
	• Patients' and investigator's satisfaction with study medication (efficacy)
	• Recommendation of study drug to others and willingness to use the medication in the future

Safety	Safety endpoints: • Type, frequency, severity and assessment of drug relationship of reported treatment-emergent adverse events (AEs) • Tolerability of the study medication (assessed by patient and investigator) • Percentage of patients requiring further medication for treatment of acute pharyngitis after end of study • Percentage of patients with an increase in throat pain intensity [NRS score points] or difficulty in swallowing [mm VAS] at Visit 2 compared to baseline (Visit 1, t0) requiring further medication
Statistical methods	The analysis of the primary endpoint was performed applying a GEE model using logit as link function (SAS proc genmod) for

	binary response and treatment as factor. Study centre was included as confounding factor into the model. Except for the primary endpoint, all analyses and statistical tests for the difference between treatment groups were performed in an exploratory manner. Statistical tests were performed two-sided using an α-level of 5 % (type I error rate). Continuous variables were described by medians and mean values. Standard deviation, quartiles, minimum and maximum were used as indices of dispersion. Categorical variables were described in contingency tables as absolute numbers and percentages. The number of AEs and the number and percentage of patients with at least one AE were tabulated for each treatment group by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA, Version 19.1). The number of patients with at least one drug-related AE (ADR) was compared between treatment groups using Fisher's exact test. The log rank test was used to compare the time to first ADR between treatment groups.
Summary of results	
Efficacy	*Primary efficacy endpoint:* Complete resolution of throat pain and difficulty in swallowing 72 hours post initial dose (p.i.d.) was achieved by 44.6% of 156 patients in the Dorithricin® group compared to 27.2% of 160 patients in the placebo group (estimated Total Responder rates for the FAS taken from the repeated measurement model [GEE]; primary endpoint based on questionnaire data collected at Visit 2). The difference in Total Responder rates of 17.4% (CI [5.8%; 29.7%]) was statistically significant in favour of Dorithricin® (GEE: p=0.0022; FAS) and corresponds to a 64% improvement in favour of Dorithricin®. The sensitivity analysis in the PP population confirmed the results (GEE: p=0.0019). *Secondary efficacy endpoints*: • Complete resolution of throat pain and difficulty in swallowing 48 hours p.i.d. and symptom free until the end of the study was achieved by 11.3% of 156 patients in the Dorithricin® group compared to 3.4% of 160 patients in the placebo group (estimated Early Responder rates for the FAS taken from the GEE model, secondary endpoint). The group difference of 7.9% (CI [1.1%;22.5%]) was statistically significant in favour of Dorithricin® (GEE: p=0.0115; FAS). The sensitivity analysis in the PP population confirmed the results (GEE: p=0.0093). • The difference in responder rates for single symptoms of acute pharyngitis (i.e. throat pain and difficulty in swallowing analysed separately, secondary endpoints) were statistically significant in favour of Dorithricin® regarding complete resolution of throat pain 72 hours p.i.d. and complete resolution of difficulty in swallowing 72 hours p.i.d. or 48 hours p.i.d. and symptom-free until study end (GEE: all p-values <0.05). The difference in the responder rates regarding complete resolution of throat pain 48 hours p.i.d. and symptom-free until study was close to statistical significance in the FAS (GEE: p=0.0528) and reached

	statistical significance in favour of Dorithricin® in the PP analysis (GEE: p=0.0485). • The baseline differences in difficulty to swallow and throat pain at Visit 2 showed a better improvement in throat pain of 0.5 NRS score points (CI [-0.1;1.0] points) and improvement in difficulty to swallow of 3.3 mm VAS (CI [-1.9;8.50] with Dorithricin® but the difference was too small to reach statistical significance in the linear mixed model (LMM) analysis in the FAS. In the PP analysis, the baseline difference in throat pain at Visit 2 was statistically significant in favour of Dorithricin® (p=0.0323). • The estimated median time to complete resolution of symptoms was comparable between treatment groups (Dorithricin® vs. placebo) for time to free of throat pain (61.0 vs. 59.1 hours p.i.d.), time to free of difficulty in swallowing (61.0 vs. 60.5 hours p.i.d), and for time to free of both symptoms (61.1 vs. 60.6 hours p.i.d.) (log rank test: all p-values >0.05). • *Symptom relief after administration of the initial dose*: ○ In both treatment groups the mean throat pain intensity and the mean intensity of difficulty in swallowing significantly decreased within 2 hours after administration of the initial dose of 2 lozenges (MMRM: p <0.0001). ○ The estimates for group differences in throat pain intensity (NRS scores) and difficulty in swallowing intensity (mm VAS) showed a statistically highly significant treatment effect with Dorithricin® from 5 to 120 minutes p.i.d. (all p-values <0.05). ○ The mean values of the sum of symptom intensity differences (SPID) in throat pain (score points*min) and difficulty in swallowing (mm*min) 1 and 2 hours after the initial dose were higher in the Dorithricin® group indicating greater reduction in pain intensity and swallowing difficulty with Dorithricin® compared to placebo at both time points (Throat pain: SPID 1 hour -108.9 vs. -78.3 points*min and SPID 2 hours -241.9 vs. -182.2 points*min; Difficulty in swallowing: SPID 1 hour -876.5 vs. -582.8 mm*min and SPID 2 hours -2068.3 vs. -1404.2 mm*min). The group differences were all statistically highly significant in favour of Dorithricin® (Wilcoxon 2-sample test: all p-values <0.005). ○ The median time to symptom relief (i.e., reduction in throat by at least 1 score point on the 11-point NRS / reduction in swallowing difficulty by at least 10 mm on 100-mm VAS) was shorter in the Dorithricin® group compared to the placebo group for both pain relief (10 vs. 15 minutes p.i.d.) and for relief in swallowing (15 vs. 30 minutes p.i.d.). The differences between groups statistically highly

	significant in favour of Dorithricin® (Log rank test: all p-values <0.005). ○ The percentage of patients with at least 50% symptom reduction from baseline was higher in the Dorithricin® group compared to the placebo group both for throat pain (23.1% vs 13.8% of patients with at least 50% NRS score reduction within 1 hour and 28.1% vs 22.6% of patients within 2 hours) and difficulty in swallowing (14.7% vs 8.1% of patients with at least 50% mmVAS reduction within 1 hour and 24.2% vs 15.8% of patients within 2 hours). The differences between groups were statistically significant (p<0.05) in favour of Dorithricin® except for the comparison of percentages achieving at least 50% NRS score reduction within 2 hours p.i.d. (GEE p=0.1857; FAS). *Additional endpoints:* • Changes in the presence and severity of signs and symptoms of acute pharyngitis calculated as TPA score were not comparable between the Dorithricin® group (N=160, 100%) and the placebo group (N=161, 100%) with regard to the percentage of patients who had an improvement (91.3% vs. 97.5%), a worsening (3.8% vs. 1.2%), or no change (2.5% vs. 0.6%) compared to baseline; data were missing for 2.5% and 0.6% of patients, respectively (Wilcoxon Rank-sum test: p=0.0014; SES). • Treatment satisfaction (ratings of 'satisfied' and 'very satisfied' combined) was higher for the 156 (100.0%) patients treated with Dorithricin® lozenges than for the 160 (100.0%) patients receiving placebo lozenges as shown by the assessments of patients (78.8% vs. 55.0%) and the investigators' assessments (78.8% vs. 55.6%) (Chi-square test: all p-values <0.005; FAS). • Patients' willingness to use the study medication in the future and to recommend the study medication to others was higher in the Dorithricin® group compared to the placebo group (75.0% vs. 47.8% and 76.9% vs. 50.9%, respectively); the differences between treatment groups were statistically highly significant (Chi-square test: all p-values <0.0001; SES).
Safety	*Treatment-emergent adverse events (TEAEs):* Overall, 42 out of 321 treated patients (13.1%) in the SES reported at least 1 TEAE irrespective of severity and causality classification. The incidence of TEAEs was higher in the Dorithricin® group (26/160 patients, 16.3%, reporting 43 TEAEs) compared to the placebo group (16/161 patients, 9.9%, reporting 25 TEAEs). Study drug related TEAEs were reported for 13/321 treated patients (4.1%), with a higher incidence in the Dorithricin® group (10/160 patients, 6.3%) compared to the placebo group (3/161 patients, 1.9%). The majority of TEAEs was mild to moderate in intensity. One patient (0.6%) in each treatment group experienced a severe TEAE.

	Common TEAEs (MedDRA PT) reported for 3 patients or more (≥1.9%) treated with Dorithricin® or placebo were headache (3.8% vs. 3.7%), nausea (1.9% vs. 1.9%), and cough (1.9% vs. 1.2%). Severe TEAEs were pneumonia (1 patient treated with Dorithricin®) and tonsillitis (1 patient receiving placebo), both considered unrelated to study drug treatment. Drug-related TEAEs (MedDRA PT) experienced in both treatment groups (Dorithricin® vs. placebo) were nausea (1.9% vs. 0.6%) and cough (0.6% vs. 0.6%); drug-related TEAEs that were only reported in the Dorithricin® group were hypoaesthesia oral (1.3% vs. 0.0%), and pharyngitis bacterial, abdominal pain upper, enteritis, dyspnoea and oropharyngeal pain (each event 0.6% vs. 0.0%). The median time to onset of the first drug-related TEAE after treatment start was longer in the Dorithricin® group compared to the placebo group (8.5 vs. 3.2 hours), but the difference between treatment groups was not statistically significant (log rank test: p=0.4513). Three (1.9%) of the 160 patients treated with Dorithricin® and 1 (0.6%) of the 161 patients treated with placebo prematurely terminated study drug treatment as a result of a TEAE. The TEAEs leading to premature termination of Dorithricin® were mild influenza like illness, mild cough and mild febrile infection (each experienced by 1 patient, 0.6% each). The TEAEs leading to premature termination of placebo were chills and pyrexia both of moderate intensity experienced by the same patient (0.6%). One patient in the Dorithricin® group experienced a serious TEAE (severe pneumonia) considered unrelated to Dorithricin®. Deaths did not occur. All TEAEs had resolved by the end of the study. *Global judgement of tolerability* The frequency of 'good' or 'excellent' ratings for tolerability of investigational treatment (both ratings combined) was comparable between the Dorithricin® group (92.5% by patients / 93.1% by investigators) and the placebo group (97.5% by patients / 98.1% by investigators) (Chi-square test p=0.3378 and p=0.1650, respectively; SES). *Need of further treatment for acute pharyngitis after end of study:* The percentage of patients requiring further medication for treatment of acute pharyngitis after study end was a little higher in the Dorithricin® group compared to the placebo group (8.8% vs. 5.6%), but the difference between treatment groups was not statistically significant (Fisher's exact test: p=0.2886). The difference between the Dorithricin® group and the placebo group was also not statistically significant regarding the percentage of patients requiring further medication due to an increase in throat pain intensity and/or difficulty in swallowing compared to baseline (2.5% vs. 1.2%; Fisher's exact test: p=0.4480; SES).
Conclusion	The results of this clinical study showed a significant benefit of Dorithricin® over placebo in the treatment of acute pharyngitis. The primary endpoint (Total Responders) and most of the secondary endpoints showed statistically significant improvements of throat pain and swallowing difficulty on Dorithricin® treatment compared with placebo:

	The percentage of total Responders in the Dorithricin® group was significantly higher 72 hours (primary endpoint) and 48 hours p.i.d. The median time to symptom relief was shorter in the Dorithricin® group compared to the placebo group for both pain relief and for relief in swallowing. The difference between groups was statistically significant in favour of Dorithricin®. Dorithricin® lozenges were well tolerated and the overall safety profile was comparable with placebo lozenges.
Date of report	15-11-2017

Subsequent substantial amendments	*Protocol Amendment No. 1, dated 04-04-2017* Inclusion criterion "pain intensity of ≥8 on a 11-point numeric rating scale" was changed to "pain intensity of ≥7 on a 11-point numeric rating scale".