Synopsis

Name of Sponsor:	Dr. Kade Pharmazeutische Fabrik GmbH Rigistraße 2 D-12277 Berlin Germany	
Name of Finished Product:	Posterisan® akut mit Lidocain 50 mg/g Rektalsalbe	
Name of Active Substance(s):	Lidocaine	

Title:	Placebo-controlled double-blind trial investigating the efficacy and tolerability of Posterisan® akut mit Lidocain 50 mg/g Rektalsalbe in abatement of complaints associated with the anorectal symptom complex	
Investigators:	Dr. med. Alex Rothhaar, Praxis Dr. Rothhaar & Colleagues, Bülowstr. 23, D-10783 Berlin, Germany A listing of all investigators is provided in Appendix.	
Study centre(s):	12 study centers in Germany.	
Publication (reference)	None as of date of report.	
Studied period: (date of first enrolment) (date of last completed)	18-JUN-2012 28-JAN-2013	Clinical Phase: III
Objectives:	To prove superior efficacy of Posterisan® akut mit Lidocain 50 mg/g Rektalsalbe in the relief of symptoms of the anorectal symptom complex compared with placebo (ointment base).	
Study design:	Prospective, multicenter, randomized, placebo-controlled, double-blind study with 2 parallel treatment arms. Generally, eligible study patients were screened and randomized at Day 0 (Baseline). The patients treated themselves at home for 3 days (Days 1-3) and completed a patient diary (for daily symptom assessment. They returned to the study site for a final assessment on Day 4 (accepted time window of +3 days).They returned to the study site for a final assessment on Day 4 (accepted time window of +3 days).	
Study population:	Adult males or females with anorectal complaints.	
Diagnosis and criteria for inclusion:	• Legally valid informed consent for study participation. • Age ≥18 years. • Patients with anorectal symptom complex (ie, pain or burning or itching).	

	• At least one of the symptoms of the anorectal symptom complex (ie, pain or burning or itching) must have an intensity of ≥65 as measured on a visual analog scale (VAS). Important exclusion criteria in terms of medical history included the presence of intra- or perianal thromboses, Grade III-IV hemorrhoids, fissures, Type IV hypersensitivity, suspected or confirmed rectal carcinoma, and chronic inflammatory bowel disease.
Test product, dose, batch number:	Posterisan® akut mit Lidocain 50 mg/g Rektalsalbe. The ointment was to be applied thinly and rubbed gently onto the affected skin and adjoining epithelium of the anal canal 2-3 times per day (single dose: maximum 2.5 g ointment containing 125 mg lidocaine) for a total treatment duration of 3 days. An applicator was optionally to be used. Used batch number was: K021251
Reference therapy, dose, batch number:	Ointment base with no active substance. The mode of application was identical as for the verum ointment. Used batch number was: K021250
Duration of treatment:	3 days (Days 1-3).
Criteria of evaluation:	
Efficacy	Note: All symptoms of the anorectal symptom complex (pain, burning, itching) were assessed by patients using a 100 mmVAS. <u>Primary efficacy endpoint:</u> • Change (improvement) from Baseline (Day 0) in the most bothersome symptom (MBS; defined as the most annoying anorectal symptom at Baseline) at the day of treatment completion (Day 3). <u>Secondary efficacy endpoints:</u> • Change (improvement) from Baseline in MBS at treatment Days 1 and 2. • Between-group comparison of MBS responder rates (response defined as an absolute value ≤30 mmVAS) at the day of treatment completion (Day 3). The preceding analyses of MBS changes were repeated separated by type of MBS (ie, by pain, burning or itching, subgroup analyses). <u>Further endpoints:</u> • Mean changes in each anorectal symptom from Baseline (Day 0) to final study assessment (Day 4).

Safety	Occurrence of local and systemic adverse events during the study period. In addition, the tolerability was assessed by patients and investigators on a 5-point ordinal scale.
Statistical methods:	Descriptive analyses: Generally, all continuous data were displayed with mean, standard deviation, extreme values, median, and 25%- and 75%-quantiles. Categorical data were described with tabulated summaries including absolute and relative frequencies. Primary efficacy analysis: The primary analysis was performed with the ITT population and applying the LOCF approach for missing values. The primary endpoint (change in MBS from Baseline [Day 0] at Day 3) was compared between treatment groups in a confirmatory fashion using the non-parametric Mann-Whitney U test (2-sided α=0.05). In addition to the precise p-value derived from this test, the effect size estimator "MWE" based on the Mann-Whitney U statistics (U/n x m; probability of concordance, with MWE=0.5 indicating maximum overlap, and the theoretical ranges of 0 and 1 indicating no overlap) with its 95% confidence intervals was provided, as well as the non-parametric Hodges Lehmann estimate (HLE) for the between-group difference in the VAS changes with its corresponding 95%-CIs. Additional sensitivity analyses to support the results of the primary efficacy analysis comprised the use of the PP population and different methods of data imputation (observed cases analysis, worst case scenario, best case scenario) in the ITT population. Secondary efficacy analyses: Changes from Baseline in MBS at treatment Days 1 and 2 were analyzed similar to the primary analysis at Day 3. The MBS responder rates were compared between treatment groups with Fisher's exact test and the Odds Ratio (OR) calculated as effect size measure. Subgroup analyses included the repetition of the pooled MBS analyses separated by type of MBS (ie, burning, itching, pain). These analyses were performed in the same way as for the main MBS analyses. Further efficacy analysis: Changes in the single symptoms of the anorectal symptom complex from Baseline at Day 4 were analyzed descriptively, but not statistically compared between treatment groups. Safety analyses: Adverse events were coded using the MedDRA terminology and summarized in frequency tables by treatment group and in total. Where applicable, Fisher's exact test was used to compare incidence rates between groups. Ordinal tolerability assessments by investigators and patients were summarized descriptively in frequency tables.

Efficacy Results:

Patient disposition:

A total of 207 patients enrolled at 12 sites entered the study, 200 received study medication and were valid for the safety and ITT analyses (103 in the Posterisan akut group and 97 in the placebo group), while 165 patients (83 Posterisan akut, 82 placebo) were valid for the PP analyses. Only one patient (placebo group) was reported to have prematurely discontinued the study (although complete data including the final visit were available for this patient).

Demographic and other baseline characteristics:

The 200 study patients (51.5% females, 48.5% males) had a mean age of 55.4 $\pm$ 13.3 years (range: 18-92 years). The most frequently reported MBS at Baseline was "itching" (74.0% of patients), followed by "burning" (18.5%) and "pain" (7.5%). Overall, there were no relevant treatment group differences at Baseline in terms of the demographic and other baseline characteristics, including symptom intensity and the distribution of the MBS.

Primary efficacy results:

The course of the MBS in the ITT population (LOCF), the change from Baseline at Day 3 and the tests for the difference in changes between treatment groups (treatment contrast) are summarized in Table A. Marked improvements from Baseline at Day 3 were seen in either treatment group, with a numerical trend towards stronger improvement on treatment with Posterisan akut compared to placebo. Based on the Hodges Lehmann estimate, the treatment contrast was 7 mmVAS in favor of Posterisan akut, and the MWE of 0.574 indicated an at least small effect in favor of Posterisan akut. However, the confirmatory statistical test (p-value from Mann-Whitney U test) and, descriptively, the 95%-CIs for the effect sizes measures (HLE and MWE) just failed to show that the observed difference is statistically significant. All sensitivity analyses yielded similar results.

Table A: Primary efficacy analysis: Changes in the MBS from Baseline (Day 0) at Day 3 (ITT, LOCF)

	Posterisan akut N=103	Placebo N=97
Day 0 (mmVAS)		
mean ± STD	79.4 ± 10.2	78.7 ± 9.7
median (min:max)	78.0 (65.0:100.0)	78.0 (65.0:100.0)
Q1 / Q3	71.0 / 85.0	70.0 / 85.0
Day 3 (mmVAS)		
mean ± STD	45.9 ± 25.5	50.8 ± 24.6
median (min:max)	47.0 (0.0:97.0)	54.0 (0.0:99.0)
Q1 / Q3	25.0 / 65.0	33.0 / 72.0
Difference (Day 0 minus Day 3)		
mean ± STD	33.5 ± 24.3	27.9 ± 24.2
median (min:max)	32.0 (-16.0:100.0)	23.0 (-15.0:85.0)
Q1 / Q3	13.0 / 54.0	8.0 / 44.0
Test statistics for difference		
p-value*	0.072	
Mann-Whitney estimator [95%-CI]†	0.574 [0.494; 0.653]	
Hodges Lehmann estimate [95%-CI]‡	7.0 [-1.0; 14.0]	

CI=Confidence interval, max=maximum, min=minimum, Q=quartile, STD=Standard deviation
*: Mann-Whitney U test.
†: Probability of concordance (calculated as U/n x m), with values >0.5 indicating a higher probability for a better outcome on Posterisan akut compared to placebo.
‡: Non-parametric estimator for the treatment contrast; ie, the difference (Posterisan akut minus placebo) in the changes from Baseline (mmVAS); asymptotic estimate for CI.

Secondary efficacy results:

- Responder rates: The results of the responder rate analyses at Day 3 were similar to the primary efficacy analysis: The responder rates (16.5% vs. 10.0% in the ITT population) and OR (0.55 in the ITT population) were in favor of Posterisan akut, but just missed to be nominally significant (p=0.079; 95%-CI for OR: [0.29; 1.05]). Results in the PP population were similar.
- Changes in MBS from Baseline at Days 1 and 2: In contrast to the Day 3 analyses, the treatment group differences for changes from Baseline at Day 1 and Day 2 in favor of Posterisan akut were nominally significant in the ITT population. On Day 1, the p-value for group differences was p=0.029 and on Day 2 the p-value was p=0.035.

Subgroup analyses:

For MBS "burning" (Posterisan akut: 19 patients, placebo group: 18 patients) and "pain" (Posterisan akut: 6 patients, placebo group: 9 patients) the results appeared to be inconclusive due to the small sample size of these subgroups. However, for the prevailing and most frequently reported MBS "itching" (78 patients in the Posterisan akut group and 70 patients in the placebo group), the treatment contrasts in favor of Posterisan akut were nominally significant ($p<0.05$) at each of the 3 assessment time points (see Table B for results at Day 3). The responder rate analysis in the ITT population among the patients with “itching” as MBS showed a nominally significant difference in favor of Posterisan akut (18.2% vs. 8.8%, p=0.041; OR=0.43, 95%-CI: [0.20; 0.92]).

Table B: Subgroup analysis: Changes in the prevailing MBS "itching" from Baseline (Day 0) at Day 3 (ITT, LOCF)

	Posterisan akut N=78	Placebo N=70
Day 0 (mmVAS)		
mean ± STD	79.1 ± 10.0	78.3 ± 9.9
median (min:max)	78.0 (65.0:100.0)	76.5 (65.0:100.0)
Q1 / Q3	70.0 / 85.0	70.0 / 85.0
Day 3 (mmVAS)		
mean ± STD	45.2 ± 25.7	52.3 ± 25.1
median (min:max)	47.0 (0.0:93.0)	55.0 (0.0:99.0)
Q1 / Q3	22.0 / 65.0	34.0 / 72.0
Difference (Day 0 minus Day 3)		
mean ± STD	33.9 ± 25.3	26.0 ± 24.9
median (min:max)	32.5 (-16.0:100.0)	22.0 (-15.0:81.0)
Q1 / Q3	15.0 / 55.0	3.0 / 44.0
Test statistics for difference		
p-value*	0.044	
Mann-Whitney estimator [95%-CI]†	0.596 [0.504; 0.688]	
Hodges Lehmann estimate [95%-CI]‡	9.0 [0.0; 17.0]	

CI=Confidence interval, max=maximum, min=minimum, Q=quartile, STD=Standard deviation
*: Mann-Whitney U test.
†: Probability of concordance (calculated as U/n x m), with values >0.5 indicating a higher probability for a better outcome on Posterisan akut compared to placebo.
‡: Non-parametric estimator for the treatment contrast; ie, the difference (Posterisan akut minus placebo) in the changes from Baseline (mmVAS); asymptotic estimate for CI.

Safety Results:

As expected due to the short observation period, the incidence of adverse events in either treatment group was rather low and similar among treatment groups (10.7% vs. 8.2%; p=0.634). Almost all of the reported AEs (19/24 events in 17/19 patients with AEs) were considered drug-related. No deaths or other serious adverse events were reported.

The most frequently reported adverse event on preferred term level in either treatment group was "diarrhea" with each 5 patients per treatment group involved. Generally, almost all of the reported adverse events in either treatment group belonged to the SOC "gastrointestinal disorders" and seemed to be associated with manifestations of the study disease, or local hypersensitivity reactions to the study treatment. The only adverse events, which were obviously not associated with diarrhea, abdominal discomfort/distension, or complaints in the rectal or anal region, were "contusion" and "back pain". Five patients (3 on Posterisan akut and 2 on placebo) had at least one severe adverse event reported. All severe and at least possibly drug-related AEs in either treatment group were completely resolved.

Local/global tolerability of the study treatment were mainly assessed by subjects and investigators to be "very good" or "good" at the end of the treatment period. Assessments of patients and investigators were almost congruent.

Overall, the AE pattern was quite similar in the 2 treatment groups, and there was no robust indication that treatment with Posterisan akut might be associated with a special risk of certain AEs compared to placebo. Thus, study treatment showed to be safe and well tolerated, and no new or unexpected safety signals were observed.

Conclusion

The formal primary efficacy endpoint (superiority in MBS improvement at Day 3) was not met, since the observed treatment group differences in favor of Posterisan akut were close to statistical significance, but eventually did not become statistically significant. However, the analyses of the treatment group differences in MBS changes at Day 1 and 2 as well as all analyses of the prevailing MBS "itching" (which concerned the vast majority of patients) consistently showed treatment contrasts in favor of Posterisan akut, which were all statistically significant ($p < 0.05$) on an exploratory level in the ITT population. Thus, the efficacy results observed in this study indicated that Posterisan akut provides an intrinsic therapeutic benefit that goes beyond the application of a plain ointment base. Additionally considering the good safety profile, the study data indicated that Posterisan akut is an effective and safe treatment option for patients suffering from anorectal complaints, especially anorectal itching.

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Appendix

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