The contribution of galenics to patients' sensory perception of nasal sprays after nasal surgery – data from a prospective randomized, controlled, double-blind, cross-over, multi-centre study

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Short Report

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The contribution of galenics to patients' sensory perception of nasal sprays after nasal surgery – data from a prospective randomized, controlled, double-blind, cross-over, multi-centre study

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ABSTRACT

Introduction:

Postoperative care after nasal surgery is commonly achieved with nasal sprays. The current study compared two decongesting, wound healing nasal sprays in patients after nasal surgery in order to investigate their sensoric perception. One of the sprays presented a new galenic formulation (*nasic® neo, Cassella-med GmbH & Co. KG*).

Methods:

Using a cross-over design, patients who had undergone nasal surgery applied two different nasal sprays during two treatment periods of 4 days each, interrupted by 3 days wash out period. Sensoric perception of the nasal sprays was assessed with the nasal-spray-sensoric-scale. Throughout the study, nasal obstruction was evaluated by patients, and physical examinations, measurements of vital parameters and rhinoscopic examinations were carried out by investigators. Adverse events were documented during the entire study, and following treatment, patients judged the overall preference, efficacy and tolerability of both products.

Results:

Overall, no significant differences in sum scores of the assessments of the nasal-spray-sensoric-scale were observed between treatments. Significant periodic effect observed during the cross-over study limited the overall analysis. Nevertheless, it could be shown that significantly more patients preferred the *new galenics* nasal spray compared to the *comparator* spray (57.1% vs. 34.7%; p=0.031). Further, 10% more patients rated the efficacy of *new galenics* as 'good' to 'very good' compared to the *comparator*. Importantly, a subgroup population of patients with more pronounced signs of inflammation present at screening evaluated the sensoric perception of *new galenics* significantly better (p=0.033) compared to the *comparator.* Within this

subgroup, no periodic effect was observed. The application of both nasal sprays was shown to be safe and well-tolerated.

Conclusion:

The current study showed that the overall sensoric perception of both nasal sprays was evaluated comparably well in patients after nasal surgery and that overall, the application of the *new galenics* nasal spray was preferred by significantly more patients compared to the *comparator* nasal spray. Patients with marked nasal abnormalities may have a greater benefit from the contribution of galenics as significant differences in the sensoric evaluation by the nasal-spray-sensoric-scale in favour of the *new galenics* product were shown for this subgroup.

Trial registration: The current study was registered in the EU Clinical Trials Register with the EudraCT No: 2019-004936-52.

Keywords: nasal-spray-sensoric-scale, nasal surgery, rhinopathia, sensoric perception, treatment satisfaction,

INTRODUCTION

The main functions of the nose are the respiration with heating and humidification of the inhaled air (air conditioning), particle filtration via the mucociliary transport system, and the olfactory function [1]. These functions are influenced by the variable cavernous tissue of the nasal septum and the nasal conchae, as the mucosa covering both structures regulates the width of the nose and its functional state.

In clinical practice, several reasons such as e.g. dysmorphoses, nasal obstruction or mucus hyperproduction may result in functional impairments of the nose, and corrections of the nasal septum and the nasal conchae, especially the lower concha, are among the most frequent surgical interventions in otorhinolaryngology [2].

Every surgical intervention represents an injury to the tissue, to which the body reacts with a constant inflammatory reaction. The aim of this is to fend off pathogenic germs, to break down necrotic tissue and to restore the tissue structurally and functionally with the help of proliferation and repair processes. After an operation on the nasal septum or the nasal conchae, post-operative symptoms such as a blocked nose, runny nose, or reduced sense of smell often occur in addition to pain and bleeding. For symptomatic treatment in the post-operative period, various active ingredients or combinations of active ingredients are recommended, including the use of saline solutions for humidification, steam inhalations, decongestants and intranasal steroid preparations.

According to the currently valid guidelines, isotonic nasal sprays or appropriate nasal rinses are used after nasal surgery to soothe the nasal mucosa, and decongestant nasal sprays and ointments can alleviate the typical symptoms of dry crust and bark formation [3]. The combination of the decongestant xylometazoline hydrochloride and the wound healing dexpanthenol has been established as standard postoperative nasal wound care over the last 20 years [4, 5]. Decongesting nasal sprays are also recommended for treatment of acute rhinitis

88 [6]. As symptoms in patients after nasal surgery and with acute rhinitis have common features
89 (as e.g. presence of nasal congestion and irritations of the nasal mucosa), treatment after nasal
90 surgery represents a good model for acute rhinitis and the results of the current study are of
91 relevance for both indications.
92 The current study aimed to compare the sensory quality of two nasal sprays containing the
93 combination of xylometazoline hydrochloride and dexpanthenol, one of which (*nasic® neo*)
94 additionally contained the excipient hyaluronic acid resulting in a new galenic formulation
95 (detailed formulations see Materials and Methods). Based on the assumption that these changed
96 galenics have a positive impact on the sensory properties, the perception was studied in patients
97 following nasal surgery.
98
99

MATERIALS AND METHODS

Study design

The current study was a prospective, double-blind, randomized, controlled, multi-centre, cross-over trial, which was carried out in three ear nose throat outpatient centres in Germany.

The study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice (CPMP/ICH/135/1995), the study protocol, requirements of the German Medicines Act (AMG), the Basic Data Protection Regulation (DSGVO) and other applicable regulatory requirements.

Study patients and treatments

Female or male patients (18 to 64 years) with post-operative nasal breathing disorders after surgery on the nasal septum or the nasal conchae were eligible to participate in the trial. Details of in- and exclusion criteria as well as allowed and forbidden medications are listed in Table S1. After signing an informed consent, patients were randomly allocated to treatment sequence 1 (*new galenics*, followed by *comparator* treatment) or 2 (*comparator* treatment, followed by *new galenics*; see Figure 1). Randomization was ensured by block randomization with a block length of 6, and randomization lists were transferred to an external pharmacy for packaging of the investigational products. Patients were assigned ascending treatment numbers in chronological order of appearance at the trial site, and investigational products were applied by patients according to the assigned treatment sequence.

Treatment was applied in crossover design: the respective first nasal spray was applied for 4 days (days 0-3 / treatment period 1), followed by a washout period of 3 days (days 4-6), continued by application of the second nasal spray for another 4 days (days 7-10 / treatment period 2, see Figure 1). During the treatment periods, patients applied the nasal sprays upon

demand but maximal 1 spray per nostril 3 times a day; during the washout period, patients did not use any of the investigational products.

The investigational medicinal product (IMP) used in the trial was the nasal sprays *nasic® neo* (hereafter referred to as *new galenics*) (containing the active ingredients xylometazoline hydrochloride [1 mg/mL] and dexpanthenol [50 mg/mL] and the excipients potassium dihydrogen phosphate, sodium monohydrogen phosphate dodecahydrate, sodium hyaluronate and purified water; Klosterfrau Berlin GmbH [manufacturer], Cassella-med GmbH & Co. KG [marketing authorization holder]). The *comparator* product was the nasal spray *NasenDuo®* (containing the active ingredients xylometazoline hydrochloride [1 mg/mL] and dexpanthenol [50 mg/mL] and the excipients potassium dihydrogen phosphate, disodium hydrogen phosphate and water for injection; Merckle GmbH [manufacturer], ratiopharm GmbH [marketing authorization holder]). Products were blinded by the external provider Hubertus Apotheke am Salzufer (Berlin), and study products were indistinguishable regarding their appearance, taste, and odour.

Study duration and assessments

The study duration for each patient was 11 days, comprising 4 site visits (V1-V4, see Table S2). During each visit, the investigators carried out a physical examination covering the general health status, ear nose throat (ENT) area (assessed by endoscopic rhinoscopy) and lungs/thorax. The status of each parameter was evaluated as ‘normal’ or ‘abnormal’ and existing abnormalities had to be described and documented by the investigators. The presence and severity of nasal edema, secretion and redness were investigated by rhinoscopy and evaluated by the rhinoscopy score ranging from 0 = absent to 3 = severe symptom. In addition, blood pressure and heart rate were measured at all visits.

148 The level of nasal obstruction was assessed by patients during each visit (prior to application
149 of a study product) on a visual analogue scale (VAS) ranging from 'no obstruction' to 'worst
150 obstruction'.
151
152 ***Nasal-spray-sensoric-scale and overall assessments***
153 To assess sensoric perceptions of the nasal sprays, patients completed paper-based
154 questionnaires depicted as visual analogue scales (VAS) reflecting the validated nasal-spray-
155 sensoric-scale (NSSS) developed by Mösges et al [7]. In addition to the given 14 items of this
156 scale, one additional item was queried (intensity of aftertaste 15 minutes after nasal spray
157 application). Completion of the questionnaires was done immediately (10 items), 2 minutes (4
158 items) and 15 minutes (1 item) after nasal spray administration (see
159 Figure ***2***). At V1 and V3, patients applied the first daily dose of the nasal spray assigned in
160 accordance with the allocated treatment sequence at the investigational site. Patients were
161 allowed to use their nasal spray at home before attending V2 or V4 but had to apply one spray
162 at the site prior to completion of the questionnaire.
163 During the final study visit (V4), patients performed a final evaluation of treatments by judging
164 the overall efficacy and tolerability of the two nasal sprays from 0 (not satisfactory) to 3 (very
165 good) and by evaluating which of the two nasal sprays had been preferred (nasal spray applied
166 during days 0-3 or during days 7-10).
167
168 ***Study endpoints***
169 The primary endpoint of the study was the difference in the total score of the sensory
170 assessments of the NSSS (14 items) after first application of either *new galenics* or *the*
171 *comparator*. The differences between the two nasal sprays were analysed independently of each
172 other in cross-over design in the assessments at V1 und V3 at the respective first application of
173 the nasal sprays (inter-group-differences). Results of the NSSS were analysed separately for the
174 first 14 items and for all 15 items.
175 Therefore, intra-individual nasal sensoric sum score differences within each treatment sequence

were assessed and averaged. A value greater than 0 indicates an evaluation in favour of the *new galenics*, a value less than 0 indicates an evaluation in favour of the *comparator* product.

Secondary endpoints included the individual (15 items) sensory assessment of the nasal-spray-sensoric-scale at first application.

Clinical effects were evaluated by analysis of changes in nasal obstruction, rhinoscopy scores and patients' overall assessment of efficacy and preference. Safety and clinical tolerability of nasal sprays were assessed by documentation of adverse events and by patients' overall judgement of product tolerability.

Statistical analysis and sample size determination

All statistical tests were performed bilaterally at the 5% significance level. Frequencies and percentages of categorial variables such as mean values and standard deviations for continuous variables were reported descriptively. Analyses were performed with the SAS for Windows 9.4 software. The primary endpoint as well as other continuous parameters were analysed using a random effect model with the terms 'patient', 'treatment', 'sequence' and 'period'. The patient was considered a random term. The student t-test and associated t-test were used to study effects of treatment sequences and groups.

For the calculation of the sample size, NSSS scores of 1200±200 for the *new galenics* and of 1100±200 for the *comparator* were assumed. Taking into account an alpha error of 0.05, a power of 0.9 and a correlation coefficient of 0.5 the total number of 44 patients was calculated, which was set to 50 considering potential drop outs.

RESULTS

Overall, 51 patients were randomised, of which 26 were allocated to treatment sequence 1 (*new galenics – comparator)* and 25 to treatment sequence 2 (*comparator – new galenics)*. All 26 patients of treatment sequence 1 completed the treatment. Within treatment sequence 2, two patients only received a single application of medication during V1, whereas 23 patients completed the treatment (see Figure 3).

The following results reflect data of the entire ITT population (randomised patients with at least complete data sets of V1 and V3, n=49) as well as data of subset populations described later.

Demographic and baseline characteristics

Demographics of participating patients are listed in Table 1. Patients aged 19 to 58 years were enrolled, and there were no statistically significant differences regarding gender, age and body mass index (BMI) between the treatment sequences.

Vital signs, physical examination

At all visits, blood pressure and heart rate of patients were documented, and values were comparable between treatment sequences. All patients presented with normal general health status and normal lung/chest values at screening visit. Abnormal ENT findings (such as e.g.; increased mucous obstruction, crusts, swelling, or oedema) were observed in a subset of patients (n=10; 38.5%; for treatment sequence 1, n=8; 34.8%; for treatment sequence 2) during the screening visit.

Nasal obstruction and rhinoscopy

Nasal obstruction values improved from V1 to V2 both upon treatment with *new galenics* (mean±SD: 40.31±21.24 to 34.77±26.25) and with *comparator* (mean±SD: 36.17±24.16 to 31.48±25.12). Within treatment sequence 1 (starting treatment with *new galenics)*, nasal obstruction values improved further, thereby reaching values of 27.38±24.23 at V3, whereas a deterioration of nasal obstruction was observed in patients of treatment sequence 2 (starting treatment with *comparator*) with values of 49.09±31.07 at V3. Thus, after treatment with the *comparator* product (including the wash-out phase) nasal obstruction worsened by a mean of 12.91 points (36.17 at V1 to 49.09 at V3). In contrast after treatment with *new galenics* (including wash-out phase) obstruction significantly improved by 12.93 (40.31 at V1 to 27.38 at V3; p=0.008) demonstrating an advantage over the comparative product (see Figure 4). Upon treatment, rhinoscopy values (sum scores including values of nasal edema, secretion and redness) improved steadily from V1 to V4 in both groups.

Sensoric perception of the applied nasal sprays

The assessment of the sensoric perception of the two nasal spray products determined by the NSSS was analysed both for the entire ITT population as well as for subgroups of patients showing abnormal findings during the ENT examination and for subgroups sorted by gender or age (below or above 30 years). Cumulative scores of the sensory evaluation of the NSSS were analysed both incorporating the first 14 items (assessment immediately and 2 minutes after application) and incorporating all 15 items (additional inclusion of assessment 15 minutes after application).

Importantly, a significant period effect was observed during the study (p=0.004) with both products being evaluated significantly better in the second period than in the first period. The thereof resulting limitations on the crossover evaluation of the endpoints were considered for the following study results.

Regarding the primary endpoint, the analysis of NSSS data (14 items) demonstrated overall, no significant treatment effect, i.e., no differences of mean sum scores were demonstrated (p=0.487, Figure 5A).

Analysis of 15 item data confirmed the results above.

Within the subgroup of patients with nasal abnormalities (pronounced signs of inflammation; n=10 for treatment group 1, n=8 for treatment group 2), no significant periodic effect was observed. Mean NSSS sum scores (14 items) after first application were 1149.5 upon *new galenics* application compared to mean NSSS sum scores of 1146.6 for the *comparator* product in treatment sequence 1. In treatment sequence 2, mean NSSS sum scores (14 items) after respective first application were 1261.63 upon *new galenics* application compared to mean NSSS sum scores of 1120.75 for the *comparator* product. Overall, statistically significantly higher NSSS values were shown upon first application of *new galenics* compared to *comparator* (p=0.033; see Figure 5B).

Subgroup analyses considering gender of patients did not show any significant treatment effects (men p=0.733; women p=0.575 considering 14 items). A significant treatment effect in favour of *new galenics* was shown for patients aged <30 years (p=0.018 in the 14-item analysis) but not for patients aged above 30 years (p=0.099 in the 14-item analysis).

The analysis of the secondary endpoints of the study investigated differences of sum scores of the NSSS over the course of the study (from V1 to V2 and from V3 to V4). No significant differences between treatment sequences were shown neither for treatment period 1 (p=0.688) nor for treatment period 2 (p=0.923).

Evaluation of single item scores

The analysis of inter-sequence comparisons for individual sensoric items revealed no significant differences between treatment sequences in none of the assessed items but a significant periodic effect in 8 out of the 14 items.

Analysis of single items of the NSSS revealed the greatest treatment differences of ≥ 4 score points for the items 2 ('amount of medication that runs into the throat or nose'), 5 ('odour intensity'), and 7 ('taste intensity') in favour of the *new galenics* product. Differences between the *new galenics* and the *comparator* product were 6.3 for item 2, 4.1 for item 5 and 6.2 for item 7. The sum of those 3 items increased significantly greater after treatment with the *new galenics* product compared to treatment with the *comparator* product (p=0.023).

The item 'nasal moisturization' improved by 4.5 points (73.27 to 77.38) during the treatment with the *new galenics* compared to improvement of 1.85 points (77.38 to 79.23) during the treatment with the *comparator* (treatment sequence 1). In treatment sequence 2, there was an improvement of 8.96 points (71.43 to 80.39) during the treatment with the *new galenics* compared to an improvement of 0.78 points (70.7 to 71.43) during the treatment with the *comparator*. While no significant differences between treatments were shown for improvement of nasal moisturization in both treatment sequences (based on cross-over design; see Figure 1), the improvement of nasal moisturization was significant only after treatment with *new galenics* during period 2 (V3-V4) (p=0.026, see Figure).

Preference of treatments

At the end of the study, patients evaluated which of the nasal spray was preferred. In total, a significantly higher number of patients (n=28; 57.1%; p=0.031) preferred the *new galenics* product over the *comparator* product (n=17; 34.1%). The remaining 4 patients (8.2%) had no preference (see Figure 7).

293

294 ***Efficacy and tolerability assessment***

295 As shown in Figure 8, the efficacy of both treatments was judged as good to very good by the
296 majority of patients. Numerical values of percentages of patients with a good or very good
297 rating of *new galenics* (85.7%) were about 10% higher than those of *comparator* (75.5%);
298 however, differences were not statistically significant (p=0.307).
299 The tolerability of both nasal sprays was evaluated as good by patients of both treatment groups
300 without significant differences.

301

302 ***Safety results***

303 No serious adverse event occurred during the trial. A total of six adverse events (AEs) in five
304 patients were documented (3 mild, 1 moderate, 2 severe intensity), one of which (nasal burning)
305 was rated as related to treatment with *comparator*, two AEs (both epistaxis) were rated as
306 probably related to treatment (1 with *new galenics*, 1 with *comparator*). All three AEs can be
307 classified as expected, as they are listed in the SPCs of the products. The relationship for the
308 other AEs was rated as unlikely or not related (see Table 2).

309

310

DISCUSSION

The current study investigated the sensory perception of two decongesting nasal sprays, *new galenics* and *comparator,* in patients during convalescence from surgery on the nasal septum or nasal conchae. While the literature has shown the positive contribution of dexpanthenol to xylometazoline containing decongestant nasal sprays [8-10] the current trial investigated the comparison of two decongestant sprays with or without the additional excipient hyaluronic acid. The sensoric perception was assessed with the validated nasal-spray-sensoric-scale (NSSS) [7], which had already been successfully applied in other studies [11]. Starting at least one week after surgery, patients were randomly assigned to 4 days treatment with one of the study products, and after 3 days wash out period, patients were crossed over to 4 days treatment with the alternative study product.

The evaluation of the nasal sensory quality after the first application of the nasal spray showed that no significant differences in NSSS sum scores could be demonstrated ($p=0.487$). Importantly, a significant period effect ($p=0.004$) was observed during the cross-over study, thereby limiting the overall analysis of results. Overall, natural healing forces proved to have more influence on the overall sensory perception of the patients than the differences in galenics. This may be considered as one of the limitations of this study.

Interestingly, a subgroup analysis including only patients with more pronounced inflammatory symptoms demonstrated that NSSS values upon first application of *new galenics* were significantly better ($p=0.033$) compared to values after first application of the *comparator* product. This result was independent of the sequence of product application (no period effect) in favour of the *new galenics* product.

A closer look at this subgroup showed that the majority of these patients was enrolled with residual abnormalities and pronounced symptoms more than 3 weeks after their nasal surgery. In contrast, the majority of “normal” patients started their study participation within the first 3

weeks after surgery. This may indicate that patients, who still suffer from nasal abnormalities three weeks after their nasal surgery, may respond particularly well to the *new galenics* treatment. In these patients the healing process may have been delayed and therefore a periodic effect does not play a role.

The analysis of a subgroup of three items of the NSSS showed that the sensoric perception of the parameters 'amount of medication, that runs into the throat or the nose', 'odour intensity', and 'taste intensity' was evaluated significantly better following application of *new galenics* compared to application of *comparator*. This finding may be explained by the higher viscosity of the new product, which has been achieved by the galenics of the new formulation. The higher viscosity of the formulation may increase the retention time of the nasal spray on the nasal mucosa, thereby decreasing the amount of spray running down nose or throat, which in turn will be perceived as less intense in taste and odour.

In line with the results above, treatments with *new galenics* resulted in an increased perception of nasal moisturization in both treatment periods with changes between V3 and V4 (treatment period 2) being statistically significant ($p=0.026$). It is likely that the new galenics contribute to those beneficial effects on the perception of moisturization over time.

At the beginning of period 2, both treatment sequences also differed in the parameter obstruction, with a clear advantage of the treatment sequence that was pre-treated with *new galenics* and then received the *comparator* in period 2. Obstruction, measured as the patient's subjective assessment on a VAS scale, described the condition at the time of the examination. The assessment was made before the application of the respective nasal spray. This is another point that could have contributed to the period effect.

Literature data support these results demonstrating that the application of products with similar galenics following sinus surgery improved functional recovery and nasal edema and crusting [12, 13].

The patients' final evaluation demonstrated a statistically significant preference for the *new galenics* product, which was perceived more pleasant by 57% (p=0.031) compared to the *comparator* product. In line with this, a greater proportion of patients (85.7 %) assessed the efficacy of the *new galenics* product as 'good to very good' compared to that of the *comparator* product (75.5%). This finding is of particular importance as patient preference clearly plays a role in treatment compliance, as described in several studies investigating the sensory perceptions of intranasal corticosteroid sprays [12-15].

CONCLUSION

In summary, the current study demonstrated the safe application of the *new galenics* product in patients after nasal surgery. Importantly, the product was perceived more pleasant compared to the *comparator* product, which may be due to the changed galenics of the formulation. As a result, fewer amounts of medication may run down throat or nose and may lead to decreased intensities of product odour and taste perception. Particularly patients with nasal abnormalities may benefit from the product as results demonstrated clear advantages for the *new galenics* treatment in this population.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJ) criteria for authorship for this article, take responsibility for the integrity of the work and have given their approval for this manuscript to be published.

Author contributions

JL, LR, LE and RM designed the study. LE and LR coordinated the study. JL participated in the conduct of the study. CB conducted the study as lead investigator. JS performed the data management and contributed to the data analysis. RM interpreted the results of the study. All authors contributed to the writing of the manuscript and approved of the final version.

Medical writing, editorial and other assistance

Writing and editorial assistance in the preparation of this manuscript was provided by Dr. Nina Werkhäuser (ClinCompetence Cologne GmbH). Assistance in MedDRA coding and editorial assistance was provided by PD Dr. Esther Raskopf (ClinCompetence Cologne GmbH).

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Compliance with ethics and guidelines

The state received a positive vote from the ethics committee of the Ärztekammer Nordrhein (medical council North Rhine, reference number 2020061).

The study was registered in the EU Clinical Trials Register with the EudraCT No: 2019-004936-52.

The study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice (CPMP/ICH/135/1995), the study protocol, requirements of the German

Medicines Act (AMG), the Basic Data Protection Regulation (DSGVO) and other applicable regulatory requirements.

All patients provided informed consent prior to participating in this study.

No data identifying single patients were included in this study, therefore, informed consent for publication is not needed.

Data availability

The data generated during and/or analysed during the current study are available from the sponsor on reasonable request.

REFERENCES

1. Ciprandi G, Gelardi M. Open and clean: the healthy nose. Acta Biomed. 2019;90(2-s):4-6.
2. Matthias C. Surgery of the nasal septum and turbinates. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2007;6:Doc10.
3. AWMF. Formstörungen der inneren und / oder äußeren Nase. S2k-Leitlinie 017/070: AWMF online; 2016.
4. Kehrl W, Sonnemann U. [Improving wound healing after nose surgery by combined administration of xylometazoline and dexpanthenol]. Laryngorhinootologie. 2000;79(3):151-4.
5. Klocker N, Verse T, Rudolph P. [The protective effect of dexpanthenol in nasal sprays. First results of cytotoxic and ciliary-toxic studies in vitro]. Laryngorhinootologie. 2003;82(3):177-82.
6. Greiner AN, Meltzer EO. Overview of the treatment of allergic rhinitis and nonallergic rhinopathy. Proc Am Thorac Soc. 2011;8(1):121-31.
7. Mösges R, Pasch N, Sayar A, Schmalz P, Vent J. [Survey of sensory perception and patients' subjective assessment of the application of nasal sprays - the nasal-spray-sensoric-scale]. Laryngorhinootologie. 2009;88(9):587-91.
8. Mösges R, Shah-Hosseini K, Hucke HP, Joisten MJ. Dexpanthenol: An Overview of its Contribution to Symptom Relief in Acute Rhinitis Treated with Decongestant Nasal Sprays. Adv Ther. 2017;34(8):1850-8.
9. Kehrl W, Sonnemann U. [Dexpanthenol nasal spray as an effective therapeutic principle for treatment of rhinitis sicca anterior]. Laryngorhinootologie. 1998;77(9):506-12.
10. Kehrl W, Sonnemann U, Dethlefsen U. [Advance in therapy of acute rhinitis--comparison of efficacy and safety of xylometazoline in combination xylometazoline-dexpanthenol in patients with acute rhinitis]. Laryngorhinootologie. 2003;82(4):266-71.
11. Hahn C, Böhm M, Allekotte S, Mösges R. Tolerability and effects on quality of life of liposomal nasal spray treatment compared to nasal ointment containing dexpanthenol or isotonic NaCl spray in patients with rhinitis sicca. Eur Arch Otorhinolaryngol. 2013;270(9):2465-72.
12. Casale M, Moffa A, Sabatino L, Pace A, Oliveto G, Vitali M, et al. Hyaluronic Acid: Perspectives in Upper Aero-Digestive Tract. A Systematic Review. PLoS One. 2015;10(6):e0130637.
13. Macchi A, Terranova P, Digilio E, Castelnuovo P. Hyaluronan plus saline nasal washes in the treatment of rhino-sinusal symptoms in patients undergoing functional endoscopic sinus surgery for rhino-sinusal remodeling. Int J Immunopathol Pharmacol. 2013;26(1):137-45.
14. Khanna P, Shah A. Assessment of sensory perceptions and patient preference for intranasal corticosteroid sprays in allergic rhinitis. Am J Rhinol. 2005;19(3):316-21.
15. Bachert C, El-Akkad T. Patient preferences and sensory comparisons of three intranasal corticosteroids for the treatment of allergic rhinitis. Ann Allergy Asthma Immunol. 2002;89(3):292-7.

FIGURES

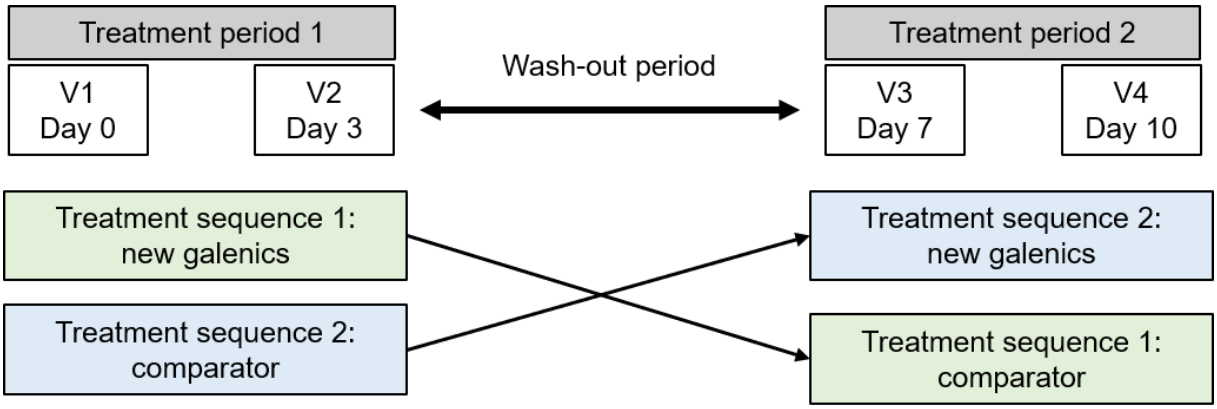


Figure 1: Cross-over design and visit time points of the trial. During the first visit (V1) on day 0, patients were randomly allocated to treatment sequences 1 or 2. Patients of treatment sequence 1 applied the *new galenics* product for the first 4 days (d0-d3) followed by a wash-out period of 3 days (d4-d6). From day 7 on (V3), patients applied the *comparator* product until day 10, where the final visit (V4) took place. Treatment group 2 applied the two nasal sprays in reverse order.

479

Immediately after application of nasal spray

1. Overall impression of the nasal spray

Not at all pleasant — Particularly pleasant

2. Amount of medication that runs into the throat or nose

Very large amount — Nothing at all

3. Extent of irritation (burning, irritation)

Very large — Not at all

4. Need to sneeze

Very pronounced — Not at all

5. Odour intensity

Very strong odour — No odour at all

6. Odour sensation

Extremely unpleasant — Very pleasant

7. Taste intensity

Very strong taste — No taste at all

8. Bitterness of taste

Very bitter — No bitterness at all

9. Taste sensation

Very unpleasant taste — Very unpleasant taste

10. Nasal moisturization

Extremely dry — Extremely moist

2 minutes after application of nasal spray

11. Intensity of aftertaste

very strong aftertaste — No aftertaste at all

12. Extent of irritation (burning, irritation)

Very large — Not at all

13. Amount of medication that runs into the throat or nose

Very large amount — Nothing at all

14. Overall impression

Not pleasant at all — Particularly pleasant

15 minutes after application of nasal spray

15. Intensity of aftertaste

very strong aftertaste — No aftertaste at all

480

Figure 2: Nasal-spray-sensoric scale (NSSS) used during the trial adapted from [7]. The validated 14-item version of the NSSS was expanded with one additional item assessed 15 minutes after nasal spray application.

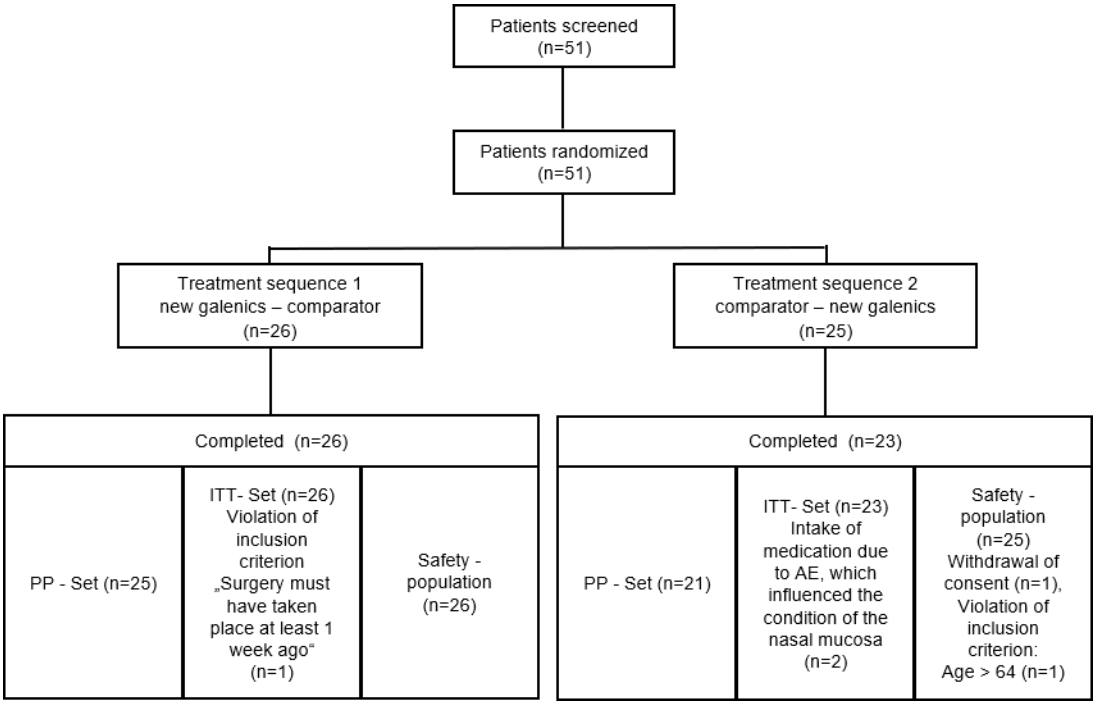


Figure 3: Allocation of patients to analysis groups. PP=per protocol population, ITT=intention to treat population (including all randomized patients with a completely documented set of nasal-spray-sensoric-scale data at V1 and V3).

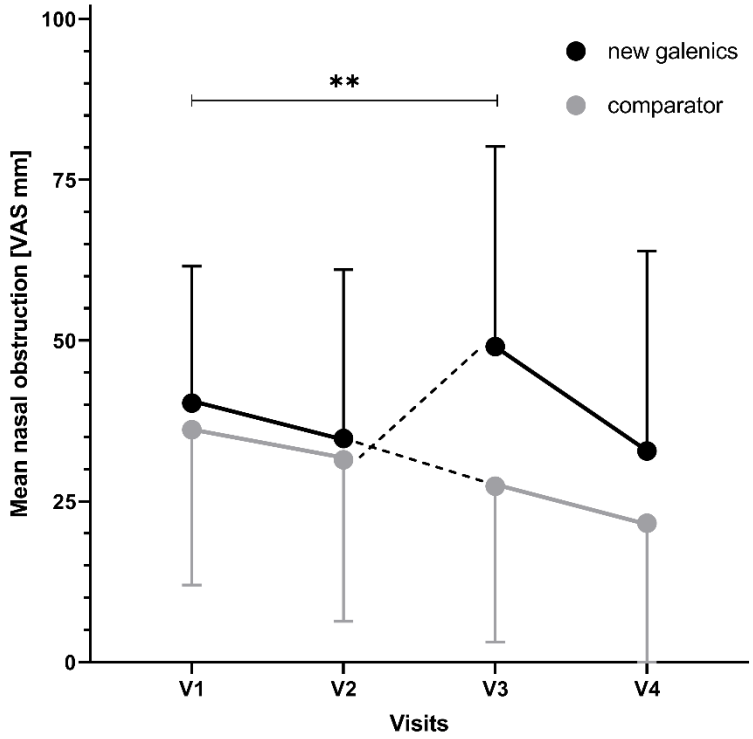


Figure 4: Change in nasal obstruction upon treatment with *new galenics* or *comparator*. Data is expressed as mean VAS + SD, with **p=0.008 for the nasal obstruction from V1 to V3 (after treatment with *new galenics*).

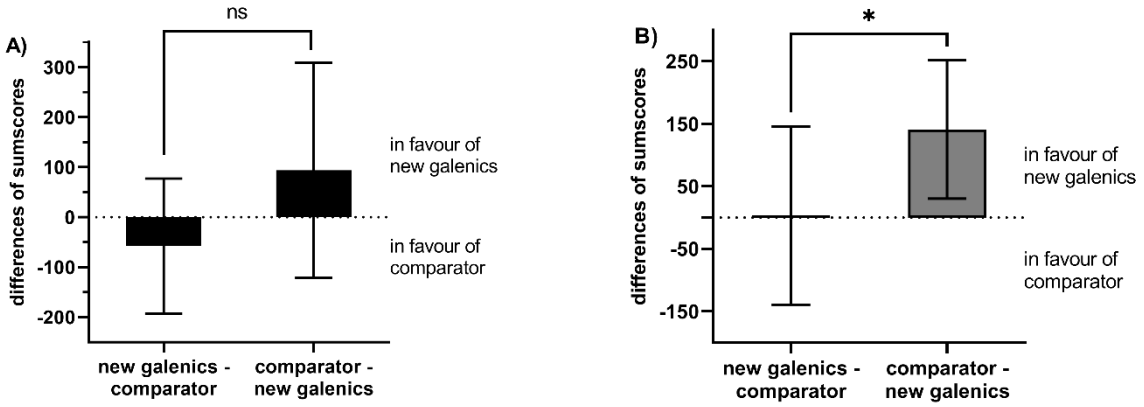
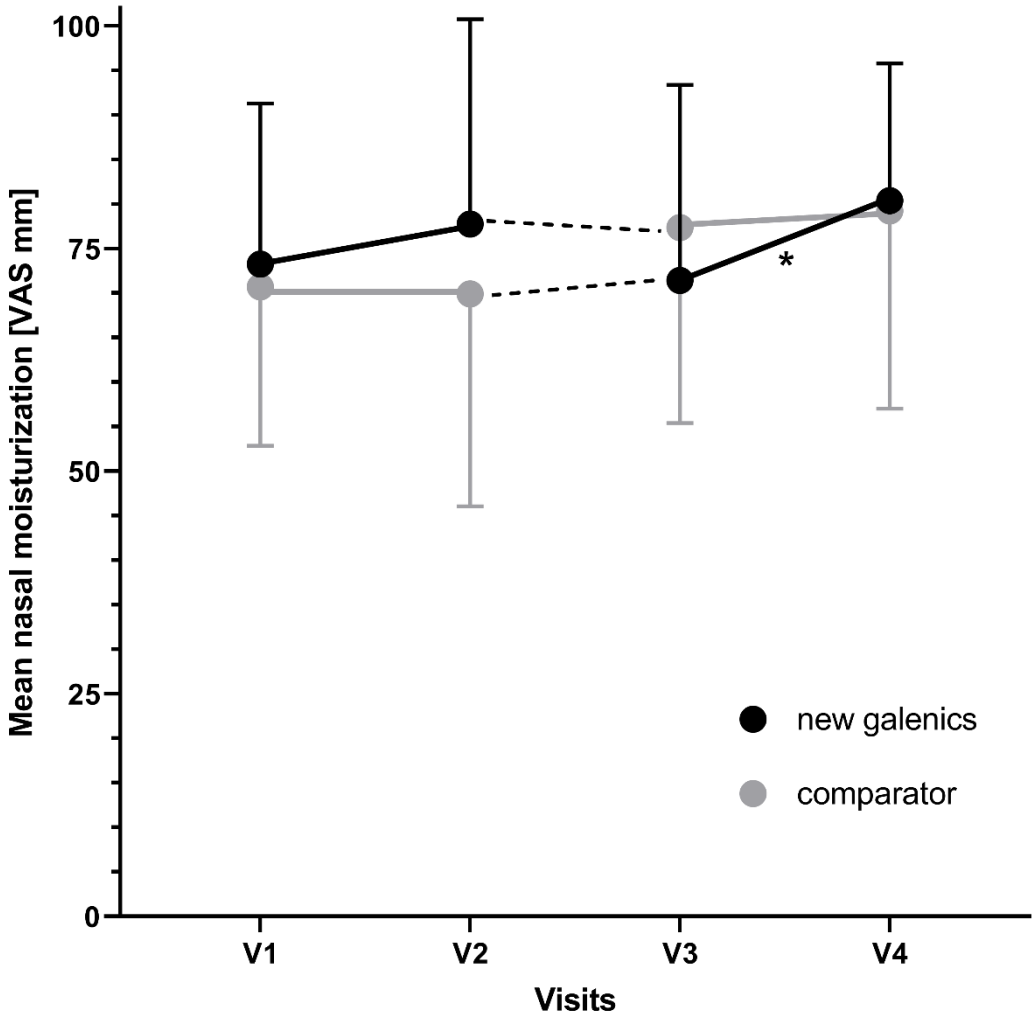


Figure 5: Mean differences of nasal sensoric sum score (NSSS) from V1 to V3. Patients were treated with *new galenics* (d0-3) followed by treatment with *comparator* (d7-10, treatment group 1) or vice versa (treatment group 2). A) analysis results of the entire ITT population

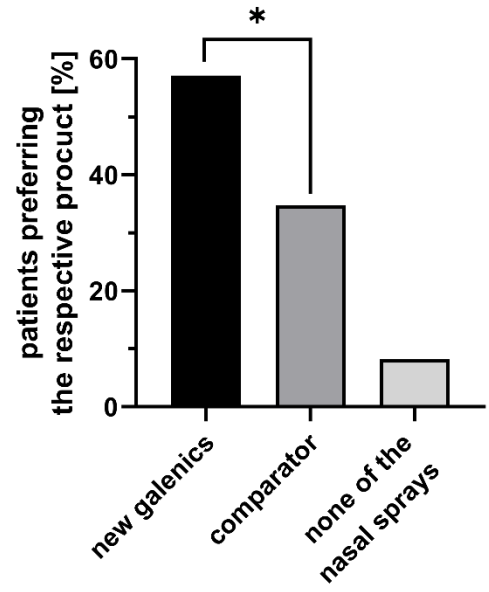
498 (n=49), B) analysis of subpopulation of patients with nasal abnormalities (n=18). Data is
499 expressed as mean difference of sum scores + SD with ns: not statistically significant and
500 *p=0.033.



501

502 **Figure 6:** Change in nasal moisturization upon treatment with *new galenics* or *comparator*.
503 Data is expressed as mean VAS + SD, with *p=0.026 for nasal moisturization from V3 to V4
504 (during treatment with *new galenics*).

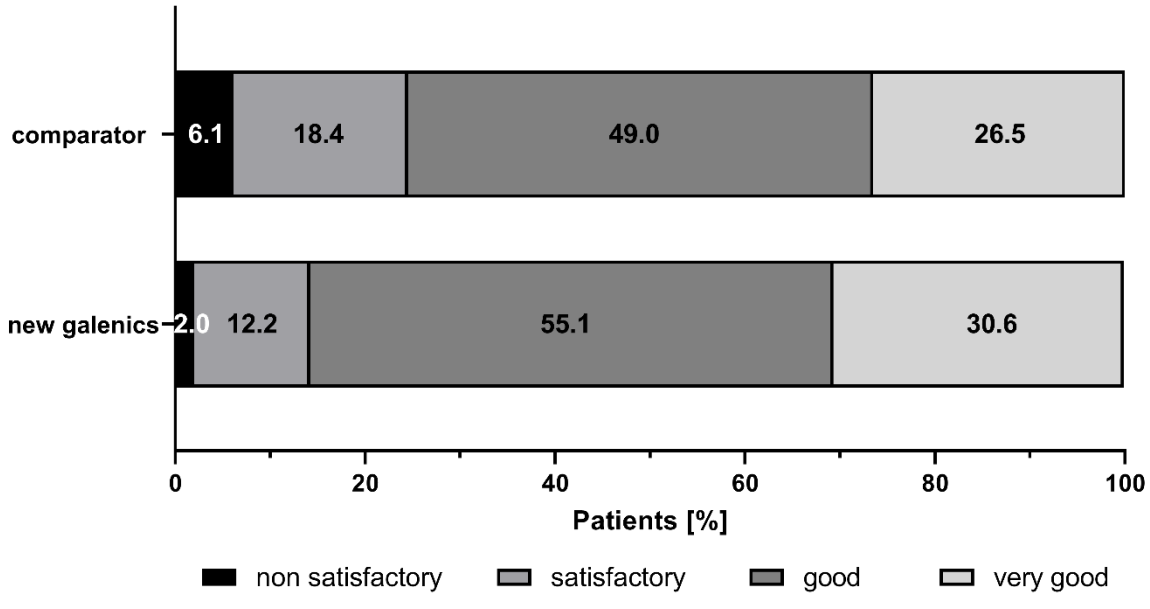
505



506

507 **Figure 7:** Preference of products assessed by patients at V4. Data is expressed as the proportion
508 if patients preferring either *new galenics*, the *comparator* or none of the two nasal sprays with
509 *p=0.031.

510



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512

513 **Figure 8:** Overall efficacy of study products assessed by patients at V4. Data is expressed as
514 the proportion of patients rating the efficacy of *new galenics* or *comparator* as either 'non-
515 satisfactory', 'satisfactory', 'good' or 'very good'.

516

517 **TABLES**

518 **Table 1:** Baseline characteristics of participants.

519

Treatment sequence			**Age [years]**	**BMI**	**Female, n (%)**	**Male, n (%)**
Treatment sequence 1 (*new galenics - comparator*)	N	valid	26	26	9 (34.60%)	17 (65.40%)
		missing	0	0		
	Mean		32.23	26.79		
	SD		10.12	4.77		
	Minimum		19	19		
	Maximum		58	37		
	Percentile	25	25.75	23.08		
		50	30.50	25.74		
		75	37.50	30.36		
Treatment sequence 2 (*comparator - new galenics*)	N	valid	23	23	10 (43.50%)	13 (56.50%)
		missing	0	0		
	Mean		32.52	26.16		
	SD		10.12	5.04		
	Minimum		20	19		
	Maximum		57	38		
	Percentile	25	24	22.44		
		50	28	25.17		
		75	41	30.19		

520

521 **Table 2:** Adverse events (AEs) documented during the study. The description of the AEs
522 represents the original wording (verbatim) translated into English.

AE description (severity)	**N (%)**	**Treatment group**	**Time of AE**	**Relationship to treatment**	**Outcome**
Headache, dizziness (mild)	1 (16.7%)	1	Wash-out phase	not related	recovered
Herpes zoster (mild)	1 (16.7%)	1	V2	not related	recovered
Disorder of tube ventilation (moderate)	1 (16.7%)	2	V2	unlikely	recovered
Epistaxis (1. severe, 2. mild)	2 (33.3%)	2	V2 V3	probably probably	recovered

Nasal burning (severe)	1 (16.7%)	2	V1	definite	recovered, premature termination
Total	6 (100%)				

523

524

525

SUPPLEMENTARY TABLES

Table S1: In- and exclusion criteria and allowed and forbidden medication of the trial.

Inclusion criteria	Exclusion criteria
Signed and dated Informed Consent Form	Current or prior (within 30 days prior to inclusion) participation in another clinical trial
Female or male patients aged 18 to 64 years	Pregnant or nursing women and women without reliable contraception
Regarding female patients: Non-pregnant, non-nursing women applying adequate contraception methods	Acute infections or epistaxis detected by endoscopic examination of both nasal cavities
Patients with post-operative nasal breathing disabilities after surgery on the nasal septum or the nasal conchae	Hypersensitivity to any ingredient of the investigational medicinal products
Surgical intervention must have taken place at least one week prior to enrolment	Presence of rhinitis sicca
	Patients undergoing surgical removal of the pituitary gland through the nose (transsphenoidal hypophysectomy) or other surgical procedures that expose the dura mater
	Patients treated with monoamine oxidase (MAO) inhibitors and other potential hypertensive drugs
	Patients treated with alpha-blockers (e.g prazosin, tamsulosin, urapidil etc.)
	Patients with increased intraocular pressure, especially glaucoma (narrow-angle glaucoma)
	Patients with severe cardiovascular diseases (e.g coronary heart disease, hypertension and long QT syndrome)
	Patients with a tumor of the adrenal gland (pheochromocytoma)
	Patients with metabolic disorders, such as hyperthyroidism and diabetes mellitus

	Patients with prostate enlargement (prostate hyperplasia)
	Addiction to alcohol or drugs
	Insufficient knowledge of the national language which endangers compliance with the regulations
Allowed medication	Forbidden medication
Non-steroidal analgesics	Any nasalia that could affect the clinical results, particularly steroids, nasal ointments, nasal rinses, and other topical decongestives
	Systemic decongestives
	Monoamine oxidase (MAO) inhibitors and other blood pressure increasing dugs
	Alpha blockers (e.g. prazosin, doxazosin, tamsulosin, urapidil, etc.)

528

529

530 **Table S2:** Study flow chart of the trial.

Visit No.	V1 Day 0	V2 Day 3	Wash-out period Day 4 - 6	V3 Day 7	V4 Day 10
Patient informed consent	x				
Check of in- and exclusion criteria	x				
Demographic data	x				
Medical history	x				
Previous medication	x				
Concomitant medication	x	x		x	x
Vital parameters	x	x		x	x
Rhinoscopy	x	x		x	x
Recording of the nasal-spray-sensoric-scale	x	x		x	x
Measurement nasal obstruction (VAS)	x	x		x	x

Pregnancy test	x				
Randomization	x				
Drug application	x------	-------		x------	-------
Dispensation of the first nasal spray	x				
Return of the first nasal spray		x			
Dispensation of the second nasal spray				x	
Return of the second nasal spray					x
Documentation of adverse events	x	x		x	x
Final evaluation					x

531