Full Research Report

Antecedents

Pannon Medisana Kft (1142, Budapest, Kassai út 130, representative: Péter Zsigmond) has inquired whether the presumed "anti-allergic" effects of the "Gyógyorr" light therapeutic device can be proven by means of scientific study.

The general purpose of the study was to assess the effectiveness and safety of the light therapeutic device in the treatment of allergic rhinitis.

During its meeting held on May 16, 2007, the Egészségügyi Tudományos Tanács Tudományos és Kutatásetikai Bizottsága [Scientific and Research Ethics Committee of the Medical Research Council] authorized, based on the documents submitted, petitioner Dr. Kristóf Nékám to conduct the non-intervention study called the *randomized, double blind, parallel group, placebo-controlled (double dummy), multicenter study for the assessment of the effectiveness and safety of Gyógyorr light therapy in the treatment of patients of various ages with allergic and non-allergic non-infectious rhinitis*, reference number 22-110/2007-1018EKU (186/PI/07.).

Scientific background

Phototherapy treatment has been utilized primarily in dermatological treatments for decades. To my knowledge, in Hungary, in vitro and clinical study results about the beneficial wound healing effects of phototherapy were first published by the working group of Professor Endre Mester in the 1970s.

In 1997, Neuman and Finkelstein reported positive results in case of allergic diseases in general and allergic rhinitis in particular in a double blind, randomized, prospective study using low-energy narrow-band (660 nm) red light phototherapy (Neuman I, Finkelstein Y.: Narrow-band red light phototherapy in perennial allergic rhinitis and nasal polyposis. Ann. Allergy, Asthma and Immunol, 78, 399-406, 1997).

In Hungary, the first report about similarly arranged studies with similarly positive therapeutic results was published by the working group of the Szegedi Tudományegyetem Bőrgyógyászati Klinika [University of Szeged, Department of Dermatology] (Koreck AI,Csoma Zs,Bodai L,Ignacz F, Szabo Kenderessy A, Kadocsa E, Szabo G, Bor Zs,Erdei A, Szony B, Homey B,Dobozy A, Kemeny L.: Rhinophototherapy: A new therapeutic tool for the management of allergic rhinitis, JACI, 115, 541-547,2005). The two studies differed primarily in the composition of the light used: 5% UV-B, 25% UV-A and 70% of visible light was the composition of the light used in the latter study. (The person who prepared this report has further detailed literature available.)

Main characteristics of the scientific study plan

The participants of the study were allergic rhinitis patients between ages 6 and 66 whose stable symptoms exceeded one third of the maximum possible points (21 points) of the total symptom score (the existence of infectious or medicamentosa rhinitis was an exclusive factor). In order to achieve real life-like results, we did not exclude patients whose symptoms became so severe as a result of some kind of medicinal treatment. In order to ensure the stability of the symptoms, we began the selection of patients around the end of the seasonal-intermittent allergy season of 2007.

The study consisted of a screening period of 7-14 days, followed by a 30-day treatment period and then a 15-day follow-up period (without treatment). The symptom journal (CRF) that was completed by the patients (their relatives) every evening included seven symptoms: itchy pharynx and/or itchy ears (notation: TNA); itchy nose (notation: TNB); runny nose (notation: TNC); sneezing (notation: TND); stuffy nose (notation: TNE); tearing (notation: TNF) and itchy eyes (notation: TNG). The range of maximum possible assignable scores was between 0 and 3 (no symptom – maximum symptom intensity). In addition, we also used the total symptom score (TTS) [translator's note: typographical error; correct: TSS] in the biometric analysis. The treatments consisted of four daily 4-5-minute light therapy sessions of both nasal passages treated simultaneously.

The primary purpose of the study was the assessment of the effectiveness and safety of the Medinose-Gyógyorr phototherapy in a randomized, double blind, parallel group, placebo-controlled (double dummy), multicenter study; the effectiveness was assessed by observing the patients using the placebo device whereas the safety factor was assessed by taking into account the unified data of all patients.

The secondary purpose of the study was the assessment, by means of a visual analog scale, of the changes in the patients' quality of life as well as in the severity of the symptoms as experienced by the patients and, furthermore, the assessment of the number of symptom-free days (further details can be found in the scientific study plan). All the parameters of the light emitted by the placebo device were consistent with those of the light emitted by the verum device, *except* for the fact that the intensity of the emitted light was approximately $1/20^{th}$ of the typical value of the verum device.

Participants

The studies were conducted at the allergy outpatient department of the Törökbálinti Tüdőgyógyintézet [County Hospital of Pulmonology, Törökbálint] (Dr. Bernadette Horváth, medical center no. 1) and of the Budai Irgalmasrendi Kórház [Buda Irgalmasrendi Hospital] (Dr. Kristóf Nékám, medical center no. 2), at the facilities of the Szakrendelo Kft, district IX (Dr. Ágnes Fényi , medical center no. 3) as well as at the Szent János Kórház Budai Egészségügyi Regionális Központ [Szent János Hospital Regional Medical Center of Buda] (Dr. Andor Hirschberg and Dr. Ágnes Fényi , medical center no.4). The device was examined by Dr. György Ábrahám at the accredited laboratory of the Budapesti Műszaki és Gazdaságtudományi Egyetem Mechatronikai, Optikai és Gépészeti Informatikai Tanszék [Deparment of Mechanical

Engineering of Mechatronics, Optics and Information Technology of Budapest University of Technology and Economics].

Statistical analysis

The biometric analysis was conducted by János Bobvos (Állami Népegészségügyi és Tisztiorvosi Szolgálat - Országos Közegészségügyi Intézet [Public Health and Medical Services – National Public Health Institute]).

Method

We aggregated the studied symptom scores used in the analysis on a weekly basis, we chose the last week of the screening period as the baseline data (time 0). In order to assess the effectiveness of the treatment, we compared the treated and not treated groups during the screening period and the weeks during and following the treatment. We applied the Kolgomorov-Smirnov test and the Shapiro-Wilk test and visually evaluated the Q-Q plots for the analysis of the distribution of the symptom values. We used the F-test and Levene's test for the analysis of the variations. Where the conditions were satisfied we used the independent two-sample t-test, where the conditions were not satisfied we used the Mann-Whitney U test. Since we observed near normal distributions in most cases, we listed the results of the t-tests as well. We applied the paired t-test and the Wilcoxon test for the study of the temporal characteristics of the symptoms. In the evaluation of the individual symptoms, we took into account only those persons who experienced the respective symptom at some point during the study. In the evaluation of the weekly frequency of the symptom-free days and of the percentage indicators we used the Chi-square test for the comparison of the groups; for the evaluation of temporal changes we used McNemar's test within groups. In case of $p<0.05$ we considered the differences to be statistically significant and, therefore, emphasized such data by using bold characters and frames. We examined the data derived from the visual analog scales (VAS) used for the assessment of the quality of life and symptom severity with similar methods; we conducted the analyses by means of the SPSS program.

Abbreviations, notations:

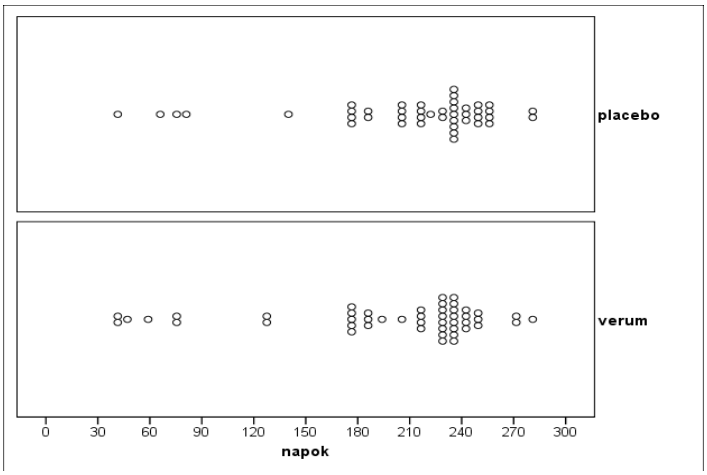
Weeks: 0 : the last week of the screening period
1-4 : weeks of the treatment period
5-6 : weeks of the follow-up period

VAS: visual analog scale, 0-10 score
TNA-TNG: the individual symptoms
TSS: total symptom score

Description of the participants in the statistical analysis:

	sex*		age group*		testing center			total
	female	male	below the age of 15	over the age of 15	1	2	3	
Verum	15	31	15	32	7	7	34	48
Placebo	12	31	11	33	6	8	30	44
Total	27	62	26	65	13	15	64	92

**Note: the database does not contain the sex of three of the participants and the age of one participant.*

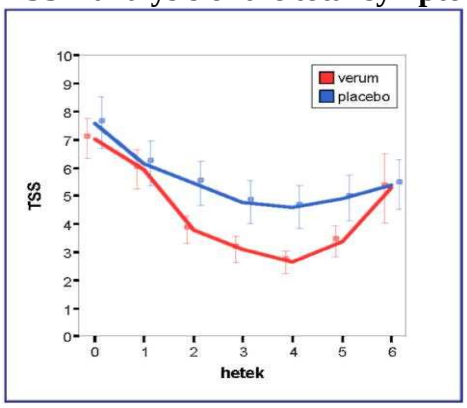


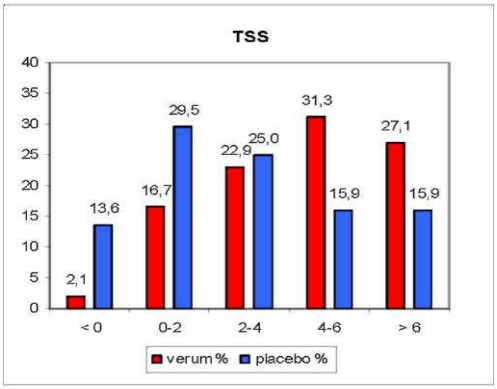
The initial day of the individual treatments in relation to August 1, 2007.
[horizontal axis: days]

The distribution of the study participants was homogenous in terms of sex and age composition and of testing centers; therefore, the disturbing effects of these factors can be ignored when conducting the analyses. Similarly, the starting time of the treatment periods of the persons involved in the study do not show significant variations in the treated and not treated groups which was also a desirable factor from the point of view of the validity of the study.

Detailed calculations

TSS – analysis of the total symptom score





Average weekly values of the total symptom scores. [horizontal axis: weeks]

Difference between the average weekly values of the total symptom scores (T4-T0) by the end of the treatment period.

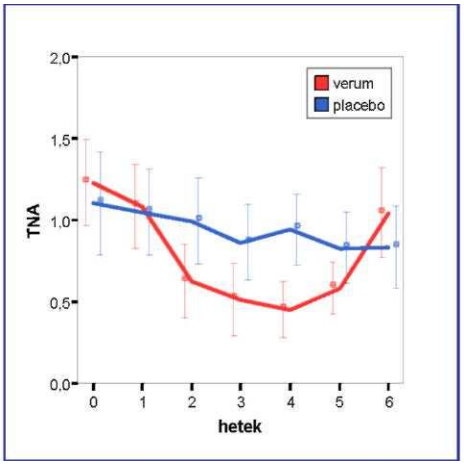
Descriptive statistics		TSS0	TSS1	TSS2	TSS3	TSS4	TSS5	TSS6
verum	number of cases	48	48	48	48	48	48	44
	average	7.04	5.96	3.79	3.10	2.64	3.39	5.28
	SD	2.47	2.37	1.67	1.62	1.41	1.95	4.05
	SE	0.36	0.34	0.24	0.23	0.20	0.28	0.61
	median	7.09	6.14	3.76	2.89	2.51	3.57	4.72
placebo	number of cases	44	44	44	44	44	44	41
	Average	7.60	6.15	5.46	4.77	4.61	4.93	5.41
	SD	2.99	2.64	2.59	2.48	2.49	2.70	2.84
	SE	0.45	0.40	0.39	0.37	0.38	0.41	0.44
	median	7.61	5.90	5.72	4.52	4.50	5.43	5.43
total	number of cases	92	92	92	92	92	92	85
	average	7.31	6.05	4.59	3.90	3.58	4.12	5.34
	SD	2.73	2.49	2.31	2.23	2.22	2.45	3.50
	SE	0.28	0.26	0.24	0.23	0.23	0.26	0.38
	median	7.37	6.07	4.41	3.54	3.07	3.88	5.29
Tests:								
T-test (independent)	p-value	0.329	0.720	**0.001**	**0.000**	**0.000**	**0.003**	0.858
difference (v-p)	Mean	-0.56	-0.19	-1.67	-1.67	-1.97	-1.54	-0.14
	95 % CI min.	0.58	0.85	-0.75	-0.79	-1.11	-0.55	1.37
	95 % CI max.	-1.71	-1.23	-2.58	-2.55	-2.82	-2.52	-1.64
Mann-Whitney test	p-value	0.437	0.815	**0.000**	**0.001**	**0.000**	**0.003**	0.728

The p-values of the Wilcoxon matched-pairs test in comparison with week 0						
N = 92	TSS1	TSS2	TSS3	TSS4	TSS5	TSS6
Ver.N=48	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**
Pl. N=44	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**

The TSS values of the first two weeks show a normal distribution; this condition is not satisfied later because of the discrepancy in the subsequent decrease of these values. There is a highly significant difference between the TSS values, which can be considered to be identical at the baseline point, during weeks 2 through 5 of the treated and not treated groups; such differences cease to exist during the second week of the follow-up period. During the fourth week of the treatment, the extent of the average improvement is a total symptom score of 1.97. There is a significant improvement in both groups during the course of the treatment as compared to the baseline week; however, with respect to the distribution based on the degree of improvement, the proportion of patients who experience an improvement that exceeds the average symptom count of the 4th week is significantly higher in the verum group -- it is twice as much as the proportion of patients in the placebo group; in addition, the increase of the symptom count is considerable in case of the placebo group participants.

The analysis of the individual symptoms

TNA - analysis of the symptoms of itchy pharynx and itchy ears



Average weekly values of the symptom scores. [horizontal axis: weeks]

Difference between the average weekly values of the symptom scores (T4-T0)by the end of the treatment period.

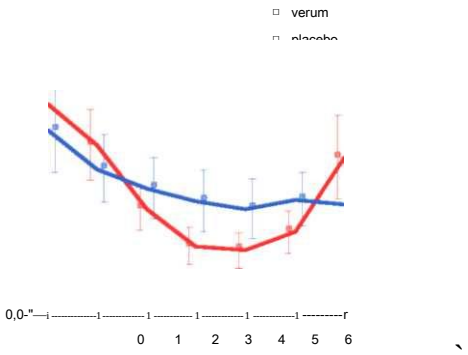
Descriptive statistics		TNA0	TNA1	TNA2	TNA3	TNA4	TNA5	TNA6
verum	number of cases	36	36	36	36	36	36	34
	average	1.23	1.09	0.63	0.52	0.45	0.59	1.05
	SD	0.78	0.76	0.67	0.66	0.51	0.48	0.79
	SE	0.13	0.13	0.11	0.11	0.09	0.08	0.13
	median	1.29	1.06	0.42	0.29	0.34	0.56	1.00
placebo	number of cases	30	30	30	30	30	30	28
	average	1.11	1.05	1.00	0.87	0.95	0.83	0.84
	SD	0.84	0.71	0.71	0.62	0.59	0.58	0.65
	SE	0.15	0.13	0.13	0.11	0.11	0.11	0.12
	median	1.03	1.01	1.04	0.86	0.96	0.91	1.00
total	number of cases	66	66	66	66	66	66	62

	Average	1.18	1.07	0.80	0.68	0.68	0.70	0.95
	SD	0.81	0.73	0.70	0.66	0.60	0.54	0.73
	SE	0.10	0.09	0.09	0.08	0.07	0.07	0.09
	median	1.10	1.02	0.71	0.47	0.50	0.71	1.00
Tests:								
T-test (independent)	p-value	0.657	0.992	**0.031**	**0.026**	**0.001**	0.077	0.257
difference (v-p)	mean	0.09	0.00	-0.39	-0.37	-0.51	-0.25	0.21
	95 % CI min.	0.50	0.37	-0.04	-0.05	-0.23	0.03	0.57
	95 % CI max.	-0.32	-0.37	-0.74	-0.70	-0.79	-0.52	-0.16
Mann-Whitney test	p-value	0.438	0.866	**0.020**	**0.006**	**0.000**	**0.044**	0.362

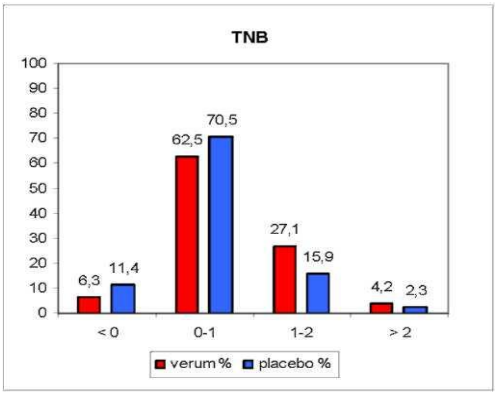
The p-values of the Wilcoxon matched-pairs test in comparison with week 0						
N = 66	TNA1	TNA2	TNA3	TNA4	TNA5	TNA6
Ver.N=36	0.056	**0.000**	**0.000**	**0.000**	**0.000**	0.114
Pl. N=30	1.000	0.513	0.367	0.414	0.069	0.056

In case of the appearance of the symptoms of itchy pharynx and itchy ears during the baseline week and during the follow-up period, the average values of the verum group are not significantly but only perceptibly higher. In spite of this, the differences between the groups during the treatment are demonstrable; a highly significant disparity develops during the 3rd and 4th weeks of the treatment. Only in case of the verum group did we observe significant improvements in comparison with the values of the baseline week. With respect to the distribution of the degree of improvement, the improvement is more significant in the verum group; in 22% of the placebo group the escalation of symptoms is also demonstrable.

TNB – analysis of the symptom of itchy nose



Average weekly values of the symptom scores. [horizontal axis: weeks]



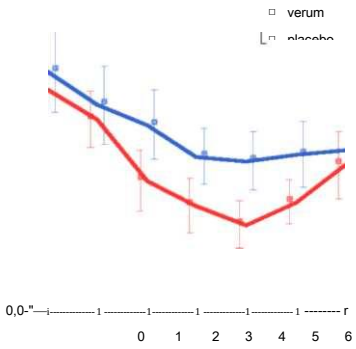
The difference between the average weekly values of the symptom scores (T4-T0) by the end of the treatment period.

Descriptive statistics		TNB0	TNB1	TNB2	TNB3	TNB4	TNB5	TNB6
verum	number of cases	42	42	42	42	42	42	39
	average	1.25	1.00	0.61	0.38	0.35	0.47	0.92
	SD	0.72	0.70	0.43	0.37	0.35	0.42	0.78
	SE	0.11	0.11	0.07	0.06	0.05	0.06	0.13
	Median	1.25	0.95	0.65	0.30	0.29	0.43	0.95
placebo	number of cases	38	38	38	38	38	38	37
	average	1.09	0.85	0.73	0.66	0.61	0.67	0.64
	SD	0.78	0.63	0.58	0.57	0.55	0.50	0.59
	SE	0.13	0.10	0.09	0.09	0.09	0.08	0.10
	median	1.06	0.91	0.79	0.68	0.59	0.76	0.61
total	number of cases	80	80	80	80	80	80	76
	average	1.17	0.93	0.67	0.51	0.47	0.56	0.78
	SD	0.75	0.67	0.51	0.49	0.47	0.47	0.71
	SE	0.08	0.07	0.06	0.06	0.05	0.05	0.08
	median	1.10	0.93	0.70	0.40	0.36	0.53	0.75
Tests:								
T-test (independent)	p-value	0.280	0.333	0.231	**0.010**	**0.013**	0.052	0.076
difference (v-p)	Mean	0.19	0.15	-0.14	-0.29	-0.27	-0.21	0.29
	95 % CI min.	0.54	0.46	0.09	-0.07	-0.06	0.00	0.60
	95 % CI max.	-0.16	-0.16	-0.37	-0.51	-0.48	-0.42	-0.03
Mann-Whitney test	p-value	0.361	0.335	0.364	**0.042**	0.079	0.054	0.114

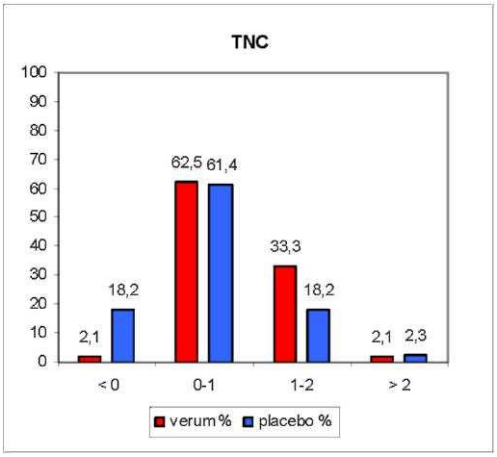
The p-values of the Wilcoxon matched-pairs test in comparison with week 0						
N = 80	TNB1	TNB2	TNB3	TNB4	TNB5	TNB6
Ver.N=42	**0.002**	**0.000**	**0.000**	**0.000**	**0.000**	**0.008**
Pl. N=38	0.118	**0.007**	**0.000**	**0.000**	**0.002**	**0.000**

The average weekly values of the symptom of itchy nose are higher in the verum group during the baseline week and at the end of the follow-up period; these values improve significantly during the 3rd week of the study period and nearly significantly during the 4th and 5th weeks in comparison with the placebo group. There is improvement in both groups as compared to the baseline week; the extent of the change is greater in case of the verum group. With respect to the distribution of the degree of improvement, improvements exceeding the average weekly score of 1 are more significant in the verum group; the frequency increase nearly doubles by the end of the treatment period.

TNC – analysis of the symptom of runny nose



Average weekly values of the symptom scores. [horizontal axis: weeks]



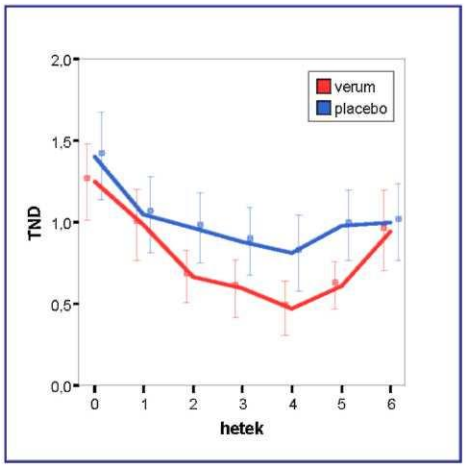
Difference between the average weekly values of the symptom scores (T4-T0) by the end of the treatment period.

Descriptive statistics		TNC0	TNC1	TNC2	TNC3	TNC4	TNC5	TNC6
verum	number of cases	47	47	47	47	47	47	43
	average	1.34	1.16	0.78	0.62	0.50	0.64	0.87
	SD	0.67	0.58	0.64	0.57	0.50	0.46	0.68
	SE	0.10	0.08	0.09	0.08	0.07	0.07	0.10
	median	1.36	1.11	0.65	0.47	0.40	0.69	0.97
placebo	number of cases	44	44	44	44	44	44	41
	average	1.44	1.23	1.08	0.89	0.86	0.91	0.94
	SD	0.81	0.77	0.69	0.56	0.58	0.65	0.69
	SE	0.12	0.12	0.10	0.08	0.09	0.10	0.11
	median	1.45	1.17	1.12	0.95	0.94	0.95	1.00
total	number of cases	91	91	91	91	91	91	84
	average	1.39	1.19	0.92	0.75	0.67	0.77	0.91
	SD	0.74	0.67	0.68	0.58	0.57	0.57	0.68
	SE	0.08	0.07	0.07	0.06	0.06	0.06	0.07
	Median	1.40	1.13	0.88	0.74	0.63	0.81	0.98
Tests:								
T-test (independent)	p-value	0.334	0.611	**0.017**	**0.008**	**0.000**	**0.030**	0.658
difference (v-p)	mean	-0.15	-0.08	-0.35	-0.33	-0.43	-0.27	-0.07
	95 % CI min.	0.16	0.22	-0.06	-0.09	-0.21	-0.03	0.23
	95 % CI max.	-0.47	-0.38	-0.63	-0.56	-0.65	-0.51	-0.36
Mann-Whitney test	p-value	0.607	0.690	**0.025**	**0.019**	**0.002**	**0.045**	0.544

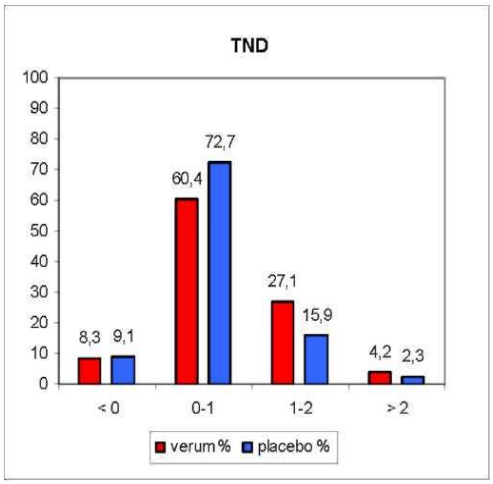
The p-values of the Wilcoxon matched-pairs test in comparison with week 0						
N = 91	TNC1	TNC2	TNC3	TNC4	TNC5	TNC6
Ver.N=47	**0.006**	**0.000**	**0.000**	**0.000**	**0.000**	**0.001**
Pl. N=44	**0.008**	**0.002**	**0.000**	**0.000**	**0.000**	**0.000**

In case of the symptom of runny nose, the average weekly values of the placebo group are slightly, not significantly higher at the end of the baseline period and of the follow-up period. A significant difference can be demonstrated between the groups during the 2-4 weeks of the treatment period and during the first week of the follow-up period; during the 4th week of the treatment the average difference is a symptom score of 0.43. There is a decrease in both groups in comparison with the baseline week; with respect to the distribution of improvements, the extent of improvement of the verum group is higher here as well. There is also an escalation of symptoms in 18% of the placebo group.

TND – analysis of the symptom of sneezing



Average weekly values of the symptom scores. [horizontal axis: weeks]



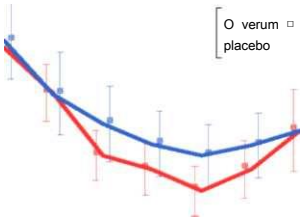
Difference between the average weekly values of the symptom scores (T4-T0)by the end of the treatment period.

Descriptive statistics		TND0	TND1	TND2	TND3	TND4	TND5	TND6
verum	number of cases	42	42	42	42	42	42	38
	average	1.25	0.99	0.67	0.60	0.48	0.62	0.95
	SD	0.75	0.70	0.51	0.56	0.53	0.46	0.75
	SE	0.12	0.11	0.08	0.09	0.08	0.07	0.12
	Median	1.36	0.98	0.60	0.47	0.37	0.66	0.95
placebo	number of cases	43	43	43	43	43	43	41
	average	1.41	1.05	0.97	0.89	0.81	0.98	1.00
	SD	0.87	0.76	0.71	0.68	0.75	0.71	0.75
	SE	0.13	0.12	0.11	0.10	0.11	0.11	0.12
	median	1.45	1.00	0.98	0.92	0.83	0.98	1.04
total	number of cases	85	85	85	85	85	85	79
	average	1.33	1.02	0.82	0.74	0.65	0.80	0.98
	SD	0.81	0.73	0.63	0.64	0.67	0.62	0.74
	SE	0.09	0.08	0.07	0.07	0.07	0.07	0.08
	Median	1.39	0.98	0.79	0.54	0.41	0.79	1.03
Tests:								
T-test (independent) difference (v-p)	p-value	0.214	0.483	**0.025**	**0.011**	**0.006**	**0.007**	0.770
	Mean	-0.22	-0.12	-0.32	-0.36	-0.41	-0.37	-0.05
	95 % CI min.	0.13	0.21	-0.04	-0.09	-0.12	-0.10	0.29
	95 % CI max.	-0.58	-0.45	-0.60	-0.63	-0.69	-0.63	-0.38
Mann-Whitney test	p-value	0.415	0.688	0.059	0.084	0.067	**0.013**	0.878

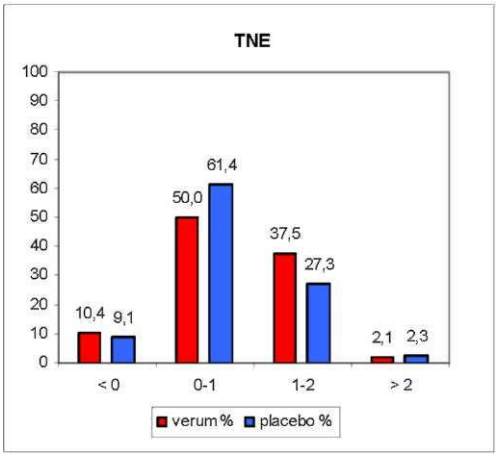
The p-values of the Wilcoxon matched-pairs test in comparison with week 0						
N = 85	TND1	TND2	TND3	TND4	TND5	TND6
Ver.N=42	**0.003**	**0.000**	**0.000**	**0.000**	**0.000**	**0.014**
Pl. N=43	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**

In case of the symptom of sneezing, the weekly average values of the placebo group were slightly, not significantly higher at the end of the baseline period and of the follow-up period. A nearly significant difference by the end of the treatment period and a significant difference during the first week of the follow-up period can be demonstrated between the groups; the average difference during the 4th week of the treatment is a symptom score of 0.41. There is a significant decrease in both groups in comparison with the baseline week; with respect to the distribution of improvement, the extent of improvement of the verum group is higher when there is a decrease that exceeds the average weekly symptom score of 1. The symptoms became more severe in some percentage of the patients.

TNE – analysis of the symptom of stuffy nose



Average weekly values of symptom scores. [horizontal axis: weeks]



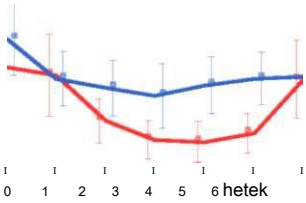
Difference between the average weekly values of the symptom scores (T4-T0) by the end of the treatment period.

Descriptive statistics		TNE0	TNE1	TNE2	TNE3	TNE4	TNE5	TNE6
verum	number of cases	47	47	47	47	47	47	43
	average	1.67	1.40	1,01	0.93	0.79	0.92	1.16
	SD	0.86	0.59	0,52	0.55	0.51	0.60	0.81
	SE	0.13	0.09	0,08	0.08	0.07	0.09	0.12
	median	1.83	1.52	1,02	0.97	0.94	0.98	1.14
placebo	number of cases	43	43	43	43	43	43	40
	average	1.71	1.39	1,20	1.08	1.01	1.07	1.16
	SD	0.77	0.83	0,75	0.65	0.62	0.64	0.63
	SE	0.12	0.13	0,11	0.10	0.09	0.10	0.10
	median	1.79	1.41	1,14	1.06	1.07	1.12	1.13
total	number of cases	90	90	90	90	90	90	83
	average	1.69	1.39	1,10	1.00	0.90	0.99	1.16
	SD	0.81	0.71	0,65	0.60	0.57	0.62	0.73
	SE	0.09	0.07	0,07	0.06	0.06	0.07	0.08
	median	1.81	1.47	1,06	1.01	1.00	1.04	1.13
Tests:								
T-test (independent)	p-value	0.673	0.768	0,100	0.103	**0.017**	0.073	0.992
difference (v-p)	Mean	-0.08	-0.05	-0,23	-0.21	-0.30	-0.23	0.00
	95 % CI min.	0.28	0.27	0,05	0.04	-0.05	0.02	0.31
	95 % CI max.	-0.43	-0.36	-0,51	-0.46	-0.54	-0.49	-0.32
Mann-Whitney test	p-value	0.987	0.554	0,253	0.198	0.074	0.209	0.927

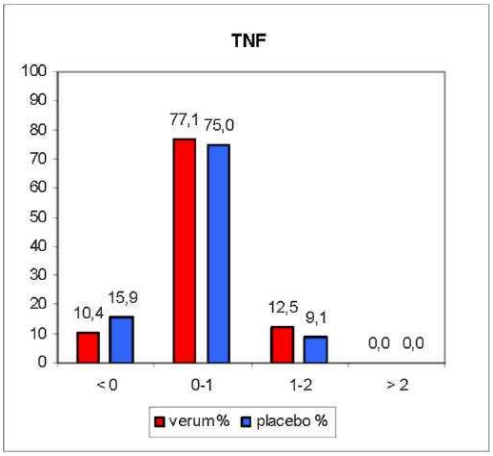
The p-values of the Wilcoxon matched-pairs test in comparison with week 0						
N = 90	TNE1	TNE2	TNE3	TNE4	TNE5	TNE6
Ver.N=47	**0.004**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**
Pl. N=43	**0.006**	**0.001**	**0.000**	**0.000**	**0.000**	**0.000**

In case of the symptom of stuffy nose, the average weekly values of the two groups at the end of the baseline period and of the follow-up period can be considered identical. A nearly significant difference can be demonstrated by the end of the treatment period; during the 4th week of the treatment the average difference is a symptom score of 0.30. There is a significant decrease in both groups in comparison with the baseline week. With respect to the distribution of improvements, the degree of improvement of the verum group is higher when there is a decrease that exceeds the average weekly symptom score of 1. The symptoms have become more severe in about 10% of the patients in both groups.

TNF – analysis of the symptom of tearing



Average weekly values of the symptom scores. [horizontal axis: weeks]



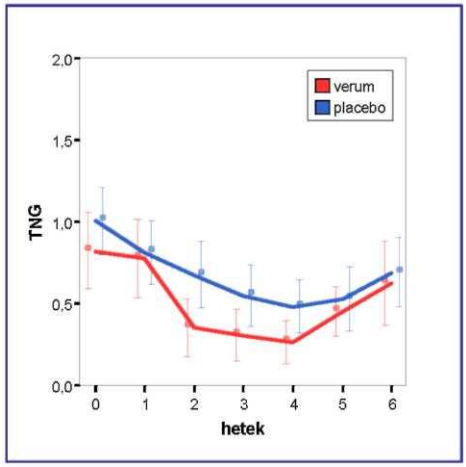
Difference between the average weekly values of the symptom scores (T4-T0) by the end of the treatment period.

Descriptive statistics		TNF0	TNF1	TNF2	TNF3	TNF4	TNF5	TNF6
verum	number of cases	32	32	32	32	32	32	30
	average	0.66	0.61	0.33	0.22	0.21	0.26	0.59
	SD	0.70	0.69	0.37	0.33	0.34	0.34	0.64
	SE	0.12	0.12	0.07	0.06	0.06	0.06	0.12
	median	0.50	0.36	0.23	0.08	0.07	0.13	0.47
placebo	number of cases	34	34	34	34	34	34	32
	average	0.84	0.59	0.54	0.49	0.55	0.59	0.61
	SD	0.65	0.48	0.49	0.57	0.50	0.46	0.48
	SE	0.11	0.08	0.08	0.10	0.09	0.08	0.08
	median	0.86	0.57	0.50	0.29	0.59	0.64	0.68
total	number of cases	66	66	66	66	66	66	62
	average	0.75	0.60	0.44	0.36	0.38	0.43	0.60
	SD	0.67	0.59	0.44	0.48	0.46	0.44	0.56
	SE	0.08	0.07	0.05	0.06	0.06	0.05	0.07
	median	0.66	0.48	0.29	0.14	0.14	0.31	0.61
Tests:								
T-test (independent)	p-value	0.307	0.969	0.068	**0.011**	**0.000**	**0.002**	0.886
difference (v-p)	mean	-0.18	-0.01	-0.21	-0.31	-0.40	-0.34	-0.02
	95 % CI min.	0.17	0.30	0.02	-0.07	-0.19	-0.13	0.27
	95 % CI max.	-0.52	-0.31	-0.43	-0.54	-0.61	-0.54	-0.31
Mann-Whitney test	p-value	0.176	0.600	0.140	**0.012**	**0.003**	**0.005**	0.575

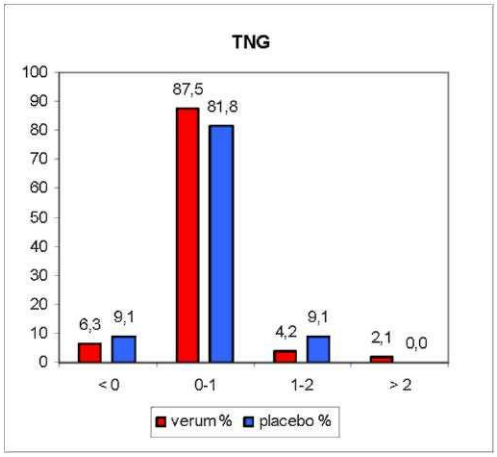
The p-values of the Wilcoxon matched-pairs test in comparison with week 0						
N = 66	TNF1	TNF2	TNF3	TNF4	TNF5	TNF6
Ver.N=32	0.118	**0.006**	**0.002**	**0.002**	**0.001**	0.364
Pl. N=34	**0.014**	**0.019**	**0.003**	**0.016**	**0.019**	**0.022**

In case of the symptom of tearing, the average weekly values of the placebo group are slightly higher at the end of the screening period. A significant difference can be demonstrated at the end of the treatment period and during the 1st week of the follow-up period; the average difference is a symptom score of 0.40 during the 4th week of the treatment. There is a significant decrease in both groups in comparison with the baseline week; in the verum group this is only the case around the middle of the study period. With respect to the distribution of improvements, there is no significant difference in the extent of improvement between the two groups, it is slightly more favorable in the verum group.

TNG – Analysis of the symptom of itchy eyes



Average weekly values of the symptom scores. [horizontal axis: weeks]



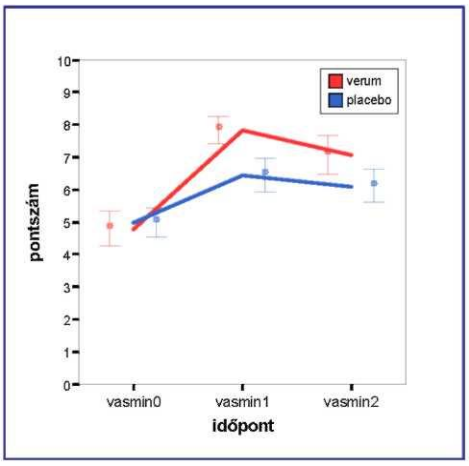
Difference between the average weekly values of the symptom scores (T4-T0) by the end of the treatment period.

Descriptive statistics		TNG0	TNG1	TNG2	TNG3	TNG4	TNG5	TNG6
verum	number of cases	31	31	31	31	31	31	30
	average	0.82	0.78	0.35	0.31	0.27	0.46	0.63
	SD	0.64	0.66	0.48	0.43	0.35	0.42	0.69
	SE	0.11	0.12	0.09	0.08	0.06	0.07	0.13
	median	0.68	0.62	0.18	0.16	0.11	0.38	0.59
Placebo	number of cases	34	34	34	34	34	34	32
	average	1.01	0.81	0.68	0.55	0.48	0.53	0.69
	SD	0.58	0.56	0.58	0.53	0.47	0.56	0.59
	SE	0.10	0.10	0.10	0.09	0.08	0.10	0.10
	median	0.96	0.77	0.69	0.45	0.43	0.41	0.79
total	number of cases	65	65	65	65	65	65	62
	average	0.92	0.80	0.52	0.44	0.38	0.50	0.66
	SD	0.61	0.61	0.55	0.50	0.43	0.49	0.63
	SE	0.08	0.08	0.07	0.06	0.05	0.06	0.08
	median	0.88	0.69	0.37	0.29	0.20	0.39	0.70
Tests:								
T-test (independent)	p-value	0.231	0.813	**0.016**	**0.048**	**0.039**	0.527	0.698
difference (v-p)	Mean	-0.18	-0.04	-0.33	-0.24	-0.22	-0.08	-0.06
	95 % CI min.	0.12	0.27	-0.06	0.00	-0.01	0.17	0.26
	95 % CI max.	-0.49	-0.34	-0.59	-0.48	-0.42	-0.32	-0.39
Mann-Whitney test	p-value	0.123	0.527	**0.020**	0.061	0.073	0.851	0.348

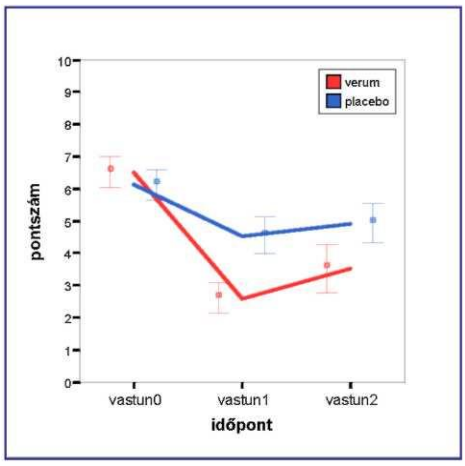
The p-values of the Wilcoxon matched-pairs test in comparison with week 0						
N = 65	TNG1	TNG2	TNG3	TNG4	TNG5	TNG6
Ver.N=31	0.198	**0.000**	**0.000**	**0.000**	**0.001**	0.061
Pl. N=34	**0.032**	**0.003**	**0.000**	**0.000**	**0.000**	**0.010**

In case of the symptom of itchy eyes, the average weekly values of the placebo group were slightly higher at the end of the baseline week and of the follow-up period. A significant difference can be demonstrated during the 2nd week of the treatment period; the difference is nearly significant during the following weeks. There is a significant decrease in both groups in comparison with the baseline week; in the verum group this decrease is significant only in the middle of the study period. With respect to the distribution of improvements, there is no significant difference in the extent of improvement of the two groups.

Analysis of the visual quality of life (vasmin) and symptom severity (vastun) scores



VAS quality of life scores at the end of the screening period, at the end of the treatment period and at the end of the follow-up period (time points 0, 1, 2)
[horizontal axis: time point; vertical axis: score]



VAS symptom severity score at the end of the screening period, at the end of the treatment period and at the end of the follow-up period (time points 0, 1, 2)
[horizontal axis: time point; vertical axis: score]

Descriptive statistics		vasmin0	vasmin1	vasmin2	vastun0	vastun1	vastun2
verum	number of cases	48	48	48	48	48	48
	average	4.79	7.83	7.06	6.50	2.60	3.52
	SD	1.86	1.46	2.07	1.69	1.66	2.57
	SE	0.27	0.21	0.30	0.24	0.24	0.37
	Median	4.78	8.11	7.52	6.81	2.28	2.72
placebo	number of cases	44	44	44	44	44	44
	average	5.00	6.45	6.11	6.11	4.55	4.93
	SD	1.49	1.69	1.62	1.51	1.90	1.99
	SE	0.23	0.26	0.24	0.23	0.29	0.30
	Median	5.12	6.35	5.81	6.13	4.86	5.36
total	number of cases	92	92	92	92	92	92
	average	4.89	7.17	6.61	6.32	3.53	4.20
	SD	1.69	1.71	1.92	1.61	2.02	2.41
	SE	0.18	0.18	0.20	0.17	0.21	0.25
	Median	4.98	7.45	6.55	6.41	3.39	4.50
Tests:							
T-test (independent)	p-value	0.553	**0.000**	**0.016**	0.250	**0.000**	**0.004**
difference (v-p)	Mean	-0.21	1.38	0.95	0.39	-1.94	-1.41
	95 % CI min.	0.49	2.04	1.72	1.05	-1.20	-0.46
	95 % CI max.	-0.90	0.72	0.18	-0.28	-2.68	-2.36
Mann-Whitney test	p-value	0.484	**0.000**	**0.006**	0.184	**0.000**	**0.004**

The p-values of the Wilcoxon matched-pairs test in comparison with week 0					
quality of life	vasmin1	vasmin2	symptom severity	vastun1	vastun2
verum	**0.000**	**0.000**	verum	**0.000**	**0.000**
placebo	**0.000**	**0.000**	placebo	**0.000**	**0.000**

The two measurement series show similar statistical characteristics with opposite signs, depending on the nature of the question. The two groups start off with the same classification status; there are highly significant differences at the end of the treatment period and of the follow-up period. The greatest difference is observed at the end of the treatment period; in case of the quality of life question the difference is a score of 1.38 while in case of the symptom severity it is 1.94. The characteristic that was judged subjectively changed significantly during the course of the study in both groups and this difference remained also at the end of the study, however, in case of the placebo group it became closer to the baseline values.

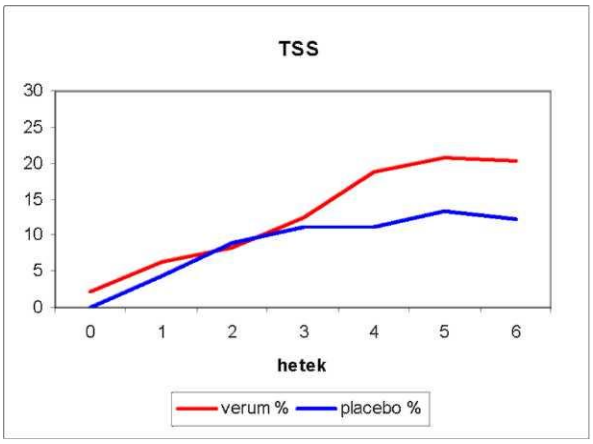
The evaluation of the symptom-free days as compared to the time prior to the start of the therapy

	weeks	TNA	TNB	TNC	TND	TNE	TNF	TNG	TSS
verum %	T0	54.2	47.9	27.1	47.9	20.8	83.3	79.2	2.1
	T1	60.4	56.3	**41.7**	**64.6**	27.1	81.3	81.3	6.3
	T2	62.5	**62.5**	**43.8**	**66.7**	29.2	83.3	83.3	8.3
	T3	64.6	**62.5**	**50.0**	**66.7**	29.2	87.5	87.5	**12.5**
	T4	**70.8**	**64.6**	**58.3**	**68.8**	29.2	**93.8**	87.5	**18.8**
	T5	**87.5**	**87.5**	**70.8**	**89.6**	**45.8**	**97.9**	**93.8**	**20.8**
	T6	54.5	54.5	**43.2**	56.8	**36.4**	77.3	86.4	**20.5**
placebo %	T0	54.5	50.0	27.3	40.9	22.7	63.6	54.5	0.0
	T1	59.1	63.6	36.4	**59.1**	27.3	**79.5**	**72.7**	4.5
	T2	60.0	61.4	**65.9**	38.6	**59.1**	**27.3**	**81.8**	**9.1**
	T3	61.4	63.6	40.9	**59.1**	25.0	**81.8**	**75.0**	**11.4**
	T4	61.4	63.6	40.9	**56.8**	25.0	**81.8**	**72.7**	**11.4**
	T5	65.9	63.6	**52.3**	50.0	**38.6**	72.7	**84.1**	**13.6**
	T6	53.7	**65.9**	**48.8**	39.0	31.7	73.2	**70.7**	**12.2**

The percent distribution of the participants as a function of the number of symptom-free days during the individual weeks (weeks 0 through 6) according to the symptoms (TNA-TNG) and to the entirely symptom-free status (TSS).

In the table, we analyzed the percent proportions of those participants who did not experience the given symptom for at least one day during the relevant week, that is, there was at least one symptom-free day. The percent proportions emphasized in bold represent the values that are significantly different within the individual group starting from the baseline week (T0) as measured by McNemar's test. The boxed percentage values show the significant differences between the verum and placebo groups as measured by the Chi-square test during the relevant time periods.

As far as the changes within the respective groups are concerned, there is a significant increase in case of each symptom in the verum group at the end of the treatment period and during the first week of the follow-up period. The incidence of symptoms increases in the placebo group as well, however, such a significant increase can be observed in case of only three symptoms at the end of the treatment period. At the baseline point, a significant difference (TNG) between the two groups occurs only in one case; further differences can be observed during the second week of the treatment period and during the first week of the follow-up period.



The percent distribution of the participants according to entirely symptom-free status (TSS) during the individual weeks (weeks 0 through 6).
[horizontal axis: weeks]

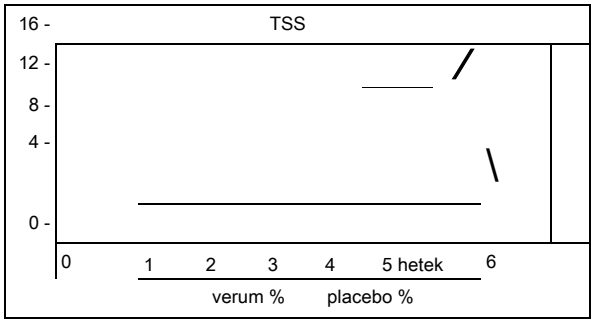
With respect to the entirely symptom-free days, a significant increase can be demonstrated – from 2.1% to 20.8% -- in the verum group by the beginning of the follow-up period. The significant increase can also be observed in the placebo group, however, this is considerably lower than in the verum group, particularly from the last week of the treatment period (T4-T5). During this interval, the difference exceeds 50%.

	Weeks	TNA	TNB	TNC	TND	TNE	TNF	TNG	TSS
verum %	T0	41,4	29,7	14,6	31,5	13,7	66,2	58,3	0,9
	T1	46,4	38,5	17,2	40,2	13,4	68,5	60,6	2,0
	T2	48,4	39,4	21,3	43,1	14,9	68,5	63,3	2,0
	T3	50,1	40,2	24,2	44,9	16,0	69,7	65,6	5,0
	T4	52,2	42,3	26,8	45,2	15,7	70,6	67,6	**9,6**
	T5	**60,6**	**61,5**	**41,4**	**53,6**	**29,4**	**83,1**	**71,7**	**10,2**
	T6	41,1	41,1	**29,7**	39,4	24,8	59,8	59,2	**14,3**
placebo %	T0	49,7	37,0	14,9	23,4	9,7	49,7	39,3	0,0
	T1	49,0	42,2	20,5	34,1	18,8	60,1	49,4	1,0
	T2	48,4	42,9	21,8	34,4	19,2	62,0	52,3	5,8
	T3	49,0	43,2	23,1	35,1	19,8	61,4	52,3	7,1
	T4	49,0	45,1	23,7	36,0	19,2	61,7	52,9	6,2
	T5	53,9	48,1	**33,1**	32,8	**24,7**	57,1	**65,9**	**8,4**
	T6	48,7	47,4	**30,8**	27,6	17,2	50,6	48,4	3,9

The percent distribution of the symptom-free days according to the individual symptoms (TNA-TNG) and the entirely symptom-free days (TSS) during the study period (weeks 0 through 6).

In the table we analyzed the percentage proportions of the total symptom-free days during the relevant week in comparison with the entirely symptom-free week. The percent proportions emphasized in bold represent the values that are significantly different within the individual group starting from the baseline week (T0) as measured by McNemar's test. The boxed percentage values show the significant differences between the verum and placebo groups as measured by the Chi-square test during the relevant time periods.

With respect to the changes within the respective groups, there was a significant increase in case of each symptom in the verum group during the first week of the follow-up period; significant increase can be observed in case of three symptoms in the placebo group. The rate of increase of the number of symptom-free days is characteristically steeper in the verum group. There is no significant difference between the two groups at the baseline point (T0); departure can be observed in case of one symptom (TNF) during the first week of the follow-up period.



The percent values of the entirely symptom-free days in the verum and placebo groups.
[horizontal axis: weeks]

The proportion of the entirely symptom-free days increases consistently in case of the verum group and, starting from the 4th week, becomes slightly more frequent as compared to the placebo group. The rate of increase remains until the end of the follow-up period while, in case of the placebo group, it decreases during the fourth week of the treatment and by the end of the follow-up period; no significant departure can be demonstrated.

Summary of the results

The average baseline symptom score V/P of *itchy pharynx and itchy ears* was: 1.23/1.11; in the verum group it gradually decreased and became significantly lower starting from the 2nd week and, as in the placebo group, the difference ceased after the end of the treatment (week 6).

The average baseline symptom score V/P of *itchy nose* was: 1.25/1.09; it was significantly lower during the 3rd week than the score observed in the placebo group.

The average baseline symptom score V/P of *runny nose* was: 1.34/1.44; in the verum group it was significantly lower during weeks 2 through 5.

The average baseline symptom score V/P of *sneezing* was: 1.25/1.41; in the verum group it was significantly lower during the 5th week.

The average baseline symptom score V/P of *stuffy nose* was: 1.67/1.71; there was no significant difference between the two groups during the entire period of the study.

The average baseline symptom score V/P of *tearing* was: 0.66/0.84; in the verum group it was significantly lower during weeks 3 through 5.

The average baseline symptom score V/P of *itchy eyes* was: 0.82/1.01; in the verum group it was significantly lower during the 2nd week than in the placebo group.

The *total baseline symptom score* V/P: 7.04/6.60; taking into account the date of all the participants, it was significantly ($p \leq 0.003$) lower in the verum group during the 2nd, 3rd, 4th and 5th weeks than in the placebo group.

The patients judged their *quality of life* to be better both at the end of the treatment and at the end of the follow-up period as compared to the baseline point prior to the treatment (V/P 4.79/5.00); on the other hand, they judged their *symptom severity* (baseline values: V/P 6.50/6.11) milder than in the placebo group.

Undesirable and highly undesirable events

No highly undesirable events occurred during the treatment or during the two-week follow-up period. During the treatment period, two patients complained about dry nose, which was of short duration and ceased spontaneously.

Summary

The following conclusions can be drawn from the above detailed and documented data:

1) The "Gyógyorr" phototherapy is generally effective and safe in the treatment of allergic rhinitis, both in males and females and in patients both below 15 years of age and over 15 years of age.

2) At least one week of treatment is needed in order for the treatment to take effect.

3) In case of stuffy nose, the effectiveness of the treatment does not differ from that observed in the placebo group. This partially defines the group of patients whose treatment is expected to yield beneficial results.

4) The milder symptoms remain for approximately one week following the discontinuation of the treatment (assuming an unchanged allergenic environment).

5) The patients have reported that the improvement of symptoms also resulted in an improved quality of life.

6) The improvements observed in the placebo group can be explained by the fact that the consequences of treatment were partially based on the subjective judgment of the patients – similarly to the vast majority of medicinal studies in connection with allergic rhinitis. This also underscores the important role of psychological factors.

7) Based on the above study it can be assumed that "Gyógyorr" phototherapy *combined with* pharmacotherapy may have an additive effect.

8) Based on the study, no conclusions can be drawn with respect to what type of changes may occur in the condition of patients experiencing severe to very severe symptoms, whether with respect to the individual symptoms or to the total symptom score, when the aforementioned parameters of "Gyógyorr" phototherapy are applied.

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Respectfully:

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