

Clinical Study Report

Final Report (period: 25.01.2021 –10.01.2022)

Title of the study

Prospektive, multi-center, single-arm, open-label, observational study for Evaluation of Performance and Safety of the BICOM optima / BICOM optima Mobil device for bioresonance treatment in patient with allergic rhino-conjunctivitis.

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7 Results

7.0 Study Initiation Date

The first subject was enrolled 25 Jan 2021.

7.1 Study Completion Date

Last patient last visit was on 10.01.2022.

7.2 Disposition of Patients

132 patients (32 children from 4 to 11 years, 100 patients from 12 years) are planned to take part in this PMCF study.

Eight study sites (see section 11.1) recruited and treated 123 patients (about 6 – 29 patients per site). For the final report, 113 patient data have been included, 111 patient data have been analyzed for the primary endpoint. When informed consent was obtained for participation in this study, 10 patients showed a dependent relationship with the investigator, which is not in accordance with the Declaration of Helsinki. Therefore, these patients were excluded from the study for most analysis.

Table 8: Disposition of patients

Disposition of Patients	Value
Number of patients, planned	132
Number of patients enrolled into the study	127
Number of patients not treated * ¹	4
Number of patients treated	123
Patients being not included in the final report (10 patients were excluded because they were not independent from site and therefore violating Declaration of Helsinki criteria.)	10
Number of patients for report:	113
- Adults, ≥ 18 years	71
- Adolescents, aged 12 – 17	14
- Children, aged 4-11	28
Patients being <u>not included</u> in the primary endpoint:	
- Patients who finished with the study (EoT), but had no further visit after the first allergy treatment* ² * ³ .	2
Number of patients for primary endpoint:	111
- Adults ≥ 18 years	69
- Youth, aged 12-17	14
- Children, aged 4-11	28
Date of inclusion of first patient (date of informed consent)	2021-01-25
Date of inclusion of last patient (date of informed consent)	2021-10-25
Date of last patient last visit (LPLV)	2022-01-10
Violations of inclusion- and exclusion criteria	None

See appendix 13.1: SAR, Table: 2-1 and raw data.

*¹ Two patients in the eCRF with no informed consent and no data and two patients not treated *² Allergy specific treatment is defined as the usage of allergy specific programs in treatment alone or in combination

with other unspecific programs. *3 One patient discontinued the treatment due to an AE. See also Table 27 and Table 28 and the other patient withdrew consent.

From 123 treated patients, 10 patients were excluded (see above). Further 2 patients had no evaluable data for treatment phase. 111 patients remain for the efficiency analyses (see section 7.6).

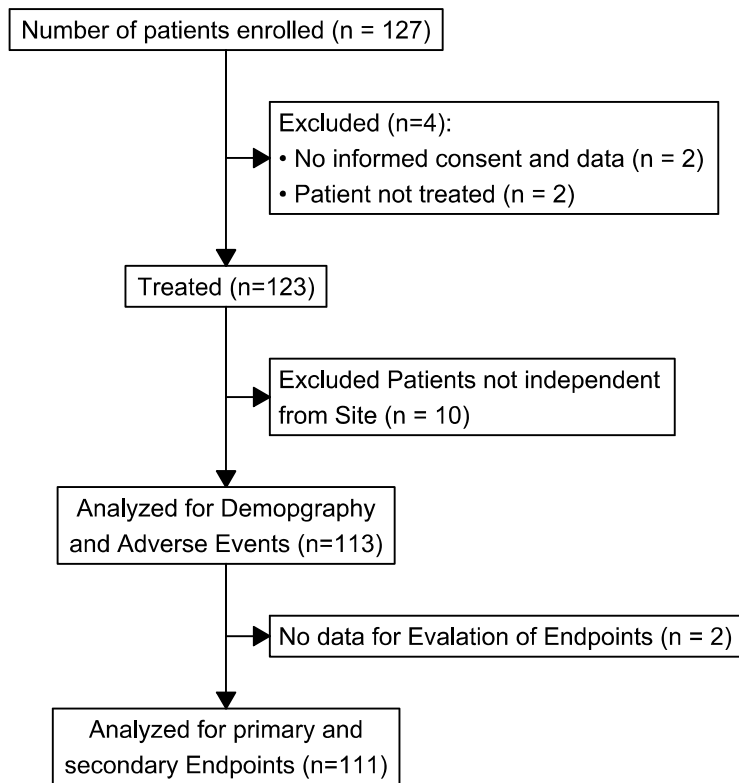


Figure 5: Disposition

7.3 Disposition of investigational Devices, Accessories and preparation Sessions

Investigational device accountability was not applicable, as this was a post-market study.

A BICOM device was installed at the study site.

7.4 Demographic and other Baseline Characteristics

7.4.1 Demographics

Demographic data for each patient were collected including sex/gender, age, height, weight and Body Mass Index (BMI). Details can be found in Table 9: .

41/113 patients (36.3%) are male, 72/113 patients (63.7%) are female patients. Patients ages ranges from 4 to 84 years; median 31 years. The patient population is composed of 71/113 adult patients (≥ 18), 14/113 youths (aged 12 to 17 years) and 28/113 children aged 4 to 11 years. More details to specific patient population (age groups) can be found in Table 9: .

Table 9: Demographics of the Study Patients

Variables	All Patients, n=113	Children aged 4-11, n=28	Youths aged 12-17, n=14	Patients (≥ 12), n=85	Adults (≥ 18), n=71
Gender					
Male	41 (36.3%)	17 (60.7%)	5 (35.7%)	24 (28.2%)	19 (26.8%)
Female	72 (63.7%)	11 (39.3%)	9 (64.3%)	61 (71.8%)	52 (73.2%)
Age (years)					
Mean	-	6.7	14.1	42.2	47.7
SD	-	2.09	1.59	20.42	17.63
Min	4	4	12	12	18
Median	31	6.5	14	43	49
Max	84	10	17	84	84
Height (m)					
Mean	-	124.3	163.3	170	171.3
SD	-	13.65	10.67	9.13	8.25
Min	95	95	140	140	156
Median	165	122	162.5	170	170
Max	192	146	183	192	192
Weight (kg)					
Mean	-	25.3	54.9	72.7	76.2
SD	-	7.64	12.98	16.54	14.88
Min	14	14	35	35	45
Median	65	23	51.5	73	77
Max	118	45	82	118	118
Body Mass Index* [kg/m²]					
Mean	-	16.1	20.4	25	25.9
SD	-	2.01	3.09	4.7	4.43
Min	13.1	13.1	16.4	16.4	17.1
Median	22.5	16	19.9	25.2	26
Max	36.4	23	26.6	36.4	36.4

*BMI is computed by the formula: weight in kilogram divided by squared height in meters.

See appendix 31.1, SAR, Table: 4-1 to Table: 4-10.

Table 10 describes the size of the residence of the patients. Most of the patients, 58/113 patients (51.3 %) live in villages with up to 20000 inhabitants. 27/113 patients (23.9 %) live in towns (20000 to 100000 inhabitants) and 28/113 patients (24.8 %) live in cities with more than 100000 inhabitants.

Table 10: Size of Residence

Size of Residence	N	Percent (%)
Up to 20000 Inhabitants	58	51.3
20000 to 100000 Inhabitants	27	23.9
More than 100000 Inhabitants	28	24.8

See appendix 13.1: SAR, Table: 4-11

7.4.2 Anamnesis of Patients

The duration of the rhino-conjunctivitis is described in Table 11. On average, patients are suffering from rhino-conjunctivitis 13.8 (\pm 15.45) years (min 0.1, max 72.6 years; median 7.8 years).

Table 11: Duration of the Rhino-conjunctivitis

Variables	Duration of Rhino-conjunctivitis [Years]
N	113
Mean	13.8
SD	15.45
min	0.1
Median	7.8
max	72.6

See appendix 313.1: SAR, Table: 5-1

As already mentioned in section 5.1, although allergic rhinitis/rhino-conjunctivitis might not appear to be serious, because it is not associated with severe morbidity and mortality compared with other medical conditions, the burden and costs are substantial, as patients had symptoms for many years.

Figure 6 describes triggers for the rhino-conjunctivitis.

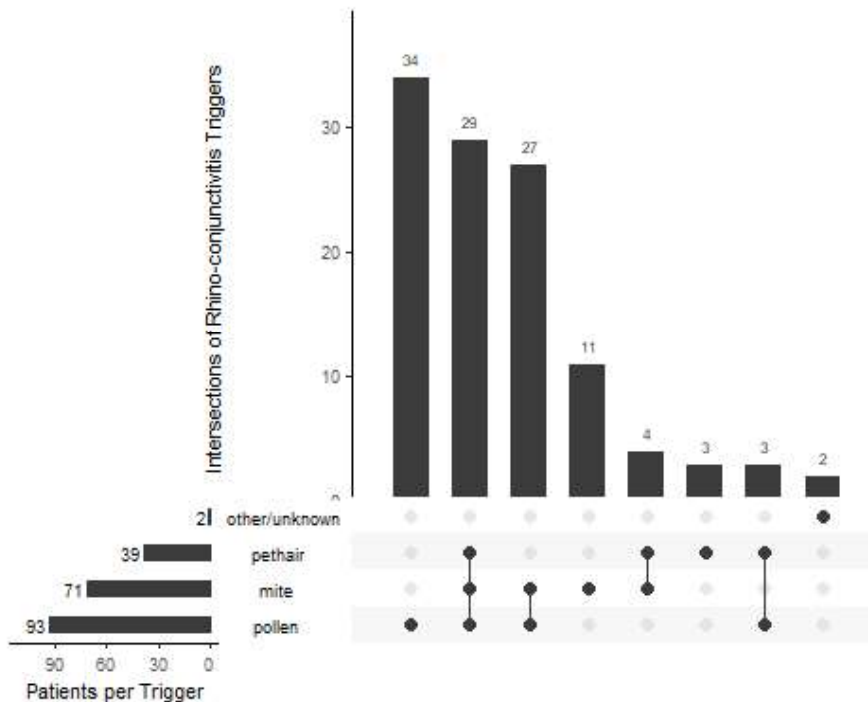


Figure 6: Known Triggers for Rhino-conjunctivitis

Main triggers for rhino-conjunctivitis are pollen, followed by house dust mite and pet hair. The majority of patients have a combination of triggers: for 27 patients, mite and pollen are triggers, for 29 patients, pet hair, mite and pollen are triggers, for 3 patients, pet hair and pollen are triggers and for 4 patients, pet hair and mite are triggers for rhino-conjunctivitis. 34 patients suffer from rhino-conjunctivitis triggered by pollen only, 11 patients by house dust mite and 3 patients by pet hair. For a small portion of patients (2 patients) the triggers of their rhino-conjunctivitis are other triggers or unknown.

See appendix 13.1: SAR, Table: 5-1

7.5 CIP Compliance

This is an observational study reflecting the clinical routine. There are no study-related procedures. The patients were treated according to the clinical routine and no protocol deviation to the treatment of the patients were observed.

7.5.1 Process of obtaining informed Consent

t During the monitoring visits at the end of the study patient enrolment period, it was observed that the process of obtaining patient consent was not performed correctly in some cases and this was documented in the monitoring visit reports as protocol deviation. The deviations were as follows:

- The consent of some children was missing, but the signatures of the parents were available.
- In the case of a 16-year-old adolescent, only the juvenile's signature was available. According to the investigator, the mother also gave her consent, but this could not be verified. This fact was documented in a Note to File.
- The investigator signed before the patient gave written consent
- For one child, parental consent was available before treatment but the child's consent was obtained only during the course of the study.
- Data was recorded in the EDC system before the signature of the patient and/or parents was obtained.
- In some case the parents signed the informed consent too late (after Visit 1), whereas the investigator has signed it already (before or during Visit 1).
- In two cases the signature of the investigator was missing by oversight, however the signatures were added retrospectively including an explanation, when this became apparent during the monitoring visit.

Due to the Corona pandemic, on-site source data monitoring occurred after the respective study site had completed enrollment. Therefore, it could only be determined that training on obtaining patient's informed consent would have been necessary for some investigators. However, data protection requirements were ensured at all times and informed consent was available from all patients and/or parents at the time of data analysis.

7.5.2 Declaration of Helsinki

When informed consent was obtained for participation in this study, 10 patients showed a dependent relationship with the investigator, which is not in accordance with the Declaration of Helsinki. Therefore, these patients were excluded from the study for most analysis. However, these 10 patients were evaluated in the sensitivity analysis (see 7.7.8). The improvement of their weekly symptom score

corresponded to the improvement of the weekly symptom score of the patients included in the analysis of the study.

7.5.3 Explorative Endpoints

The investigation of the correlation between temporal and regional pollen activity with rhino-conjunctivitis symptomatology suggested in the CIP was not included in SAP and thus not performed (chapter 9.2.4. Sensitivity analysis in the CIP). The proportion of pure pollen allergic patients is relatively small (30%) and, moreover, patients are often allergic to several pollen species. Therefore, the effort required for this (financial, logistic) could not be justified.

The subgroups listed in the CIP under exploratory analyses (Chapter 9.2.5. Exploratory analysis) were treated in the SAP under the section Sensitivity Analyses (Chapter 5.9) in the form of individual analyses. Since no substantial correlation with treatment success could be established, a multiple regression was not performed.

7.6 Study Endpoint Analysis

7.6.1 Primary Performance Endpoint

111 patients have been analyzed for primary endpoint. (see Table 12). From 123 treated patients, 10 patients were in a dependent relationship with the investigator and were excluded from the analysis. Further 2 patients had no evaluable data for treatment phase. They early quit the study. These two patients were also excluded from the analysis. That results in 111 patients available for the efficiency analyses.

The mean weekly symptom score (mean wSS) at allergy treatment compared to baseline is the primary endpoint for performance in this study.

Weekly symptom scores (wSS) are evaluated at the beginning of a visit. The wSS represents the burden of symptoms in the week before the visit. The score evaluated before the first allergy treatment session or before the first preparation treatment session, if applicable, is used as baseline. Results are then summarized in a mean weekly symptom score (Table 15).

The wSS was collected by patient questionnaires filled by patients or if the patient was a child with the help of parents or other escort before treatment. The questionnaire asks for the strongest occurrence of each of six different symptoms and the duration in days for the last seven days. The evaluated score is the sum of the product of the severity of any symptom with the number of days the symptom lasted. This sum was then divided by seven (see also section 5.1). The wSS represents the mean symptom burden in the last seven days. The lower the wSS-value the lesser was the patient's burden with symptoms.

See Table 15 for details.

Table 12: Efficacy analysis set

Disposition of Patients	Value
Number of patients, planned	132
Number of patients for primary endpoint analysis:	111
- Adults ≥ 18 years	69
- Patients ≥ 12 years	83
- Youth, aged 12-17	14
- Children, aged 4-11	28

See appendix 13.1: SAR, Table: 6-5

Allergy specific treatment is defined as the usage of allergy specific programs in treatment alone or in combination with other unspecific programs. Any visit where only combinations of unspecific treatment programs are used (programs for basic therapy, blockage-releasing and cleansing and balancing of the body are classified as preparation treatment. Mean values over treatment phase of these parameters are compared with the baseline values. Treatment phase comprise all visits after the first visit with allergy specific treatment. But also follow-up visits if available. Preparation visits after preparation baseline visit and before the first allergy treatment visit are not considered in this analysis. See Table 13.

Table 13: Type of Baseline Treatment

Type of Baseline Treatment	N	Percent (%)
Allergy treatment	56	49.6
Preparation session	57	50.4
Total	113	100

See appendix 13.1: SAR, Table: 6-1

Number of Visits in the Phase for Treatment Evaluation are shown in Table 14.

Table 14: Number of Visits in the Treatment Phase

Variable	N valid	Mean	SD	Min.	Median	Max.
Number of Visits	111	4.4	2.05	1	4	10

See appendix 13.1: SAR, Table: 6-2

On average, 4.4 visits were basis for endpoint calculations (see also section 7.7).

The wSS represents the mean symptom burden in the last seven days. The lower the wSS-value the lesser was the patient's burden with symptoms (see Table 15).

Table 15: Baseline wSS and mean wSS (treatment phase)

Symptom Scores, wSS	All Patients N = 111*1	Children aged 4-11 N = 28	Youths aged 12-17 N = 14	Patients (≥ 12) N = 83	Adults (≥ 18) N = 69
wSS (baseline)					
Mean:	7	6.3	7.3	7.2	7.2
SD	4.24	4.03	4.89	4.31	4.22
min	0	0	0.6	0	0
Median	7	6.9	6	7.4	7.9
max	15.4	14	15	15.4	15.4
Mean wSS Treatment phase					
Mean:	2.1	2	2.6	2.1	2
SD	1.64	2.01	2.32	1.51	1.3
min	0	0.1	0	0	0
Median	2	1.6	2.1	2	2
max	9	8.7	9	9	5.9

wSS = Weekly Symptom Score; *1113 patients have been included in the report. For 111 patients, endpoint analysis with all symptom and treatment data have been performed.

See appendix 13.1: SAR, Table: 6-5 to Table: 6-8.

Table 16 shows an overview on baseline wSS, mean wSS of treatment phase and the evaluated difference of baseline wSS minus the mean wSS at allergy treatment phase.

Table 16: Overview on baseline wSS, mean wSS and the difference of baseline wSS minus mean treatment phase wSS

Patient Population	Baseline wSS	Mean treatment phase wSS	Difference of baseline wSS minus mean treatment phase wSS
All Patients, N = 111			
Mean	7	2.1	4.9
SD	4.24	1.64	3.91
Min	0	0	-2
Median	7	2	5
Max	15.4	9	13.5
Children aged 4 - 11, N = 28			
Mean	6.3	2	4.3
SD	4.03	2.01	3.09
Min	0	0.1	-0.6
Median	6.9	1.6	4.7
Max	14	8.7	10.4
Youths aged 12-17, N = 14			
Mean	7.3	2.6	4.8
SD	4.89	2.32	4.11
Min	0.6	0	0.5
Median	6	2.1	4.3
Max	15	9	12.9
Patients (≥ 12), N = 83			
Mean	7.2	2.1	5.1
SD	4.31	1.51	4.14
Min	0	0	-2
Median	7.4	2	5
Max	15.4	9	13.5
Adults (≥ 18), N = 69			
Mean	7.2	2	5.1
SD	4.22	1.3	4.18
Min	0	0	-2
Median	7.9	2	5.2
Max	15.4	5.9	13.5

wSS = Weekly Symptom Score

See appendix 13.1: SAR, Table: 6-5 and 6-8 and Table: 6-11 to Table: 6-12.

7.6.2 Result t-test primary Endpoint (wSS-Score)

The primary endpoint for performance is the mean weekly Symptom Score (wSS), captured from the first treatment session after the first allergy treatment until follow-up after the last treatment visit (maximal 14 days after the last treatment visit) in the study and compared to baseline.

One hundred eleven patients provided primary outcome data for this analysis. Mean weekly symptom score (wSS) decreased from 7.0 to 2.1 points averaged on the visits, reflecting a clinically and statistically significant improvement ($p < 0.0001$, two-sided dependent t-test and 95% CI; 4.14, 5.61). The absolute change in score, which is 4.9, is clearly above the MID (1.0 points estimated in CIP, and 2 points = $\frac{1}{2}$ SD calculated from data) in wSS values and, therefore, represents a clinically significant

difference for the whole patient sample. See also Table 17 for all details and effects on the different population groups.

For all age groups the reductions in wSS are similar (Children 4.3, Youths 4.8, Patients ≥ 12 years 5.1 and Adults 5.1) and are independent highly statistically significant.

Table 17: Change of wSS – Treatment wSS compared to Baseline wSS (Mean Difference)

Statistics	wSS by all patients, N=111	wSS by Children aged 4-11, N=28	wSS by Youths aged 12-17, N=14	wSS by Patients (≥ 12), N=83	wSS by adults (≥ 18), N=69
Mean Difference	4.873	4.267	4.763	5.077	5.14
95% CI	(4.14, 5.61)	(3.07, 5.47)	(2.39, 7.14)	(4.17, 5.98)	(4.14, 6.14)
SD	3.91	3.09	4.11	4.14	4.18
t-value	13.14	7.31	4.34	11.17	10.23
DF	110	27	13	82	68
p	< 0.0001	< 0.0001	0.0008	< 0.0001	< 0.0001

See appendix 13.1: SAR, Table: 6-9 to Table: 6-10

7.6.3 Secondary Performance Endpoints

The following have been assessed as secondary endpoints:

Secondary Objectives	Endpoints for Secondary Objectives
Quality of Life (QoL), before and during the bioresonance allergy treatment	<ul style="list-style-type: none"> Mean Quality of Life Score (QoLS) as measured by a questionnaire
Mean need for medication (before and during the bioresonance allergy treatment)	<ul style="list-style-type: none"> Mean weekly medication score (wMS), at start of visit, captured from the second allergy treatment session until one week after the last allergy treatment in the study with a maximum of 8 measures compared to baseline.
Acute symptoms at the days of treatment (before and during the bioresonance allergy treatment)	<ul style="list-style-type: none"> Mean acute symptom score (aSS) at start of visit evaluated by investigator, captured from the second allergy treatment session until one week after the last allergy treatment in the study with a maximum of 8 measures compared to baseline.

The changes in QoL in patients with rhino-conjunctivitis were evaluated by assessment of a Quality of Life Questionnaire (QoLQ) and the answers to this QoLQ were collected weekly to assess the weekly QoLS. In addition, weekly Medication Score (wMS) and acute Symptom Score (aSS) are always evaluated at the beginning of a visit. The score represents the burden of medication and symptoms in the week before the visit. The wMS is evaluated with a questionnaire filled out by the patient. The aSS is evaluated by the investigator. See also Table 2 for wMS and Table 3 for aSS in section 5.1.3, respectively section 5.2.4.

In addition, the scores evaluated at the first allergy treatment session or at the first preparation treatment session, if applicable, have been used as baseline.

Quality of Life Scores (QoLS), evaluated by the QoLQ, are presented in Table 18.

7.6.4 Quality of Life Questionnaire (QoLQ) and Quality of Life Score (QoLS)

A secondary objective of this study was to evaluate the changes in health-related Quality of Life (QoL) in patients with rhino-conjunctivitis, assessed by a Quality of Life Questionnaire (QoLQ) and filled out by the patient on a weekly basis. The change in quality of life was evaluated by comparing the baseline score measured at begin of the first BICOM bioresonance treatment compared with the mean QoL-scores within allergy treatment phase. The weekly QoL-scores were captured from the first treatment session after the first allergy treatment session until follow-up after the last treatment visit (maximal 14 days after the last treatment visit) in the study and compared to baseline. The QoLQ was composed of 6 items/questions, where patients were asked to their restrictions in wellbeing, sleep, everyday activities, sports activities, school or professional activities and social contacts. A 5-point scale was used to evaluate each restriction with the following score:

- (0) Not at all (no restrictions)
- (1) A little
- (2) Slightly / a bit
- (3) Significant
- (4) Very significant

By answering the 6 questions, each week before treatment, a weekly Quality of Life score (QoLS) was captured. The mean Quality of Life Score (mean QoLS) was then compared to baseline, as secondary endpoint for efficacy. Lower values of QoLS represent fewer impairment of quality of life (see Table 18).

Table 18: Quality of Life Score (QoLS) at baseline and treatment, evaluated by the QoLQ

QoLS	All Patients N = 111*1	Children aged 4-11 N = 28	Youths aged 12-17 N = 14	Patients (≥ 12) N = 83	Adults (≥ 18) N = 69
QoLS (baseline)					
Mean:	9.4	7.1	8.7	10.2	10.5
SD	6.8	5.5	5.94	7.03	7.24
Min	0	0	2	0	0
Median	9	5.5	7.5	10	10
Max	24	16	19	24	24
Mean treatment phase QoLS					
Mean:	2.5	1.8	1.7	2.7	3
SD	2.73	2.35	1.69	2.82	2.96
Min	0	0	0	0	0
Median	1.7	1	1.3	2	2
Max	18.5	11.3	5.7	18.5	18.5
Evaluated difference: baseline QoLS minus mean treatment phase QoLS					
Mean:	6.9	5.3	7	7.5	7.6
SD	5.95	4.45	5.29	6.3	6.52
Min	-5.1	-0.3	1.9	-5.1	-5.1
Median	6	3.5	5.3	7	7.5
Max	23.3	12.8	17.3	23.3	23.3

QoLS = Quality of Life score, evaluated by a health related questionnaire filled out by the patient at each visit before the treatment

*1113 patients have been included in the report; 2 patients dropped out early and were not evaluable for primary and secondary endpoints analysis.

See appendix 13.1: SAR, Table: 6-15 to Table: 6-18 and Table 6-21 and Table 6-22.

Result of Comparison of Quality of Life at Treatment against Baseline

Table 19 shows the statistics to the evaluated difference between baseline QoLS minus the mean treatment phase QoLS for all evaluable patients as well as for the different age groups.

Table 19: Change of QoLS - Baseline QoLS minus Treatment phase QoLS (Mean Difference)

Statistics QoLS	All Patients N = 111*1	Children aged 4-11 N = 28	Youths aged 12-17 N = 14	Patients (≥ 12) N = 83	Adults (≥ 18) N = 69
Mean Difference	6.925	5.287	7.045	7.478	7.566
95% CI	(5.81, 8.04)	(3.56, 7.01)	(3.99, 10.1)	(6.1, 8.85)	(6, 9.13)
SD	5.95	4.45	5.29	6.3	6.52
t-value	12.27	6.29	4.98	10.81	9.64
DF	110	27	13	82	68
p	< 0.0001	< 0.0001	0.0002	< 0.0001	< 0.0001

See appendix 13.1: SAR, Table: 6-19 to Table: 6-20.

The evaluated mean QoLS (treatment phase) have lower values in comparison to the baseline QoLS, representing fewer impairment of quality of life during treatment phase.

7.6.5 Medication Scores (MS)

The need for medication is another secondary endpoint in this study and is evaluated with a weekly MS (see also Table 2, section 5.2).

The need for medication was evaluated with a medication score (adapted to Pfaar 2014). In this study, the MS is regarded as an indicator of BRT efficacy.

For the medication score (MS) assessment, the allergy medication intake during the week before the BICOM bioresonance treatment includes (1) oral and/or topical (eyes/nose) non-sedative H1 antihistamines, (2) intranasal glucocorticoids with/without H1 antihistamines and (3) oral glucocorticoids with/without intranasal glucocorticoids or with/without H1 antihistamines. The maximum value divided by 7 forms the (Total) weekly Medication Score (wMS).

Lower values represent fewer use of conventional medication. Most patients used no conventional medication (Table 20).

Table 20: Baseline wMS and mean wMS (treatment phase)

MS Symptom Scores	All Patients	Children	Youths	Patients	Adults
	N = 111*1	aged 4-11 N = 28	aged 12-17 N = 14	(≥ 12) N = 83	(≥ 18) N = 69
wMS (baseline)					
Mean:	0.142	0.24	0.112	0.108	0.108
SD	0.36	0.4	0.25	0.33	0.35
Min	0	0	0	0	0
Median:	0	0	0	0	0
Max	2	1	0.9	2	2
Mean wMS (treatment phase)					
Mean:	0.086	0.09	0.047	0.084	0.092
SD	0.23	0.21	0.09	0.24	0.26
Min	0	0	0	0	0
Median:	0	0	0	0	0
Max	1.3	0.8	0.3	1.3	1.3
Evaluated difference: baseline - mean wMS					
Mean:	0.056	0.15	0.065	0.024	0.016
SD	0.35	0.38	0.23	0.34	0.35
Min	-1.2	-0.8	-0.3	-1.2	-1.2
Median:	0	0	0	0	0
Max	2	1	0.7	2	2

wMS = Weekly Medication Score

*111 patients have been included in the final report; See appendix 13.1: SAR, Table: 6-35 to Table: 6-38, Table 6-41 and Table 6-42.

The evaluated data show, that conventional medication is in the observed population rare. For most visits no medication has been documented. Data are strongly skewed. Statistical results should therefore be interpreted carefully.

Result of comparison of mean weekly Medication Scores (treatment phase) against baseline

Table 21 shows the statistics for the comparison of the mean wMS (treatment phase) versus baseline wMS for all patients as well as for the different age groups.

Positive values represent an improvement respectively a reduction of symptoms.

Table 21: Change of wMS - Treatment wMS compared to Baseline wMS (mean difference)

Statistics wMS	wMS by all patients, N=111	wMS by children aged 4-11, N=28	wMS by Youths aged 12-17, N=14	wMS by Patients (≥ 12), N=83	wMS by adults (≥ 18), N=96
Mean Difference	0.056	0.15	0.065	0.024	0.016
95% CI	(-0.01, 0.12)	(0, 0.3)	(-0.07, 0.2)	(-0.05, 0.1)	(-0.07, 0.1)
SD	0.35	0.38	0.23	0.34	0.35
t-value	1.68	2.08	1.06	0.65	0.37
DF	110	27	13	82	68
p	0.0960	0.0476	0.3064	0.5151	0.7142

See appendix 13.1: SAR, Table: 6-39 and Table: 6-40.

7.6.6 Acute Symptom Score (aSS)

Before every treatment session and one week follow up after the last allergy treatment relevant for study, the actual symptoms estimated by the investigator have been collected and the acute Symptom Score (aSS) was evaluated at the day of the visit (see also Table 3 in section 5.2).

Lower values represent fewer and or weaker symptoms (see Table 22).

Table 22: aSS: Baseline, mean aSS for treatment phase and difference

Acute Symptom Scores, aSS	All Patients N = 111*1	Children aged 4-11 N = 28	Youths aged 12-17 N = 14	Patients (≥ 12) N = 83	Adults (≥ 18) N = 69
aSS (baseline)					
Mean	1.2	1	1	1.3	1.3
SD	0.78	0.71	0.7	0.8	0.81
Min	0	0	0	0	0
Median:	1	1	0.8	1.2	1.2
Max	2.8	2.8	2.3	2.8	2.8
mean aSS (treatment phase)					
Mean	0.4	0.3	0.4	0.4	0.4
SD	0.3	0.35	0.24	0.28	0.29
Min	0	0	0	0	0
Median:	0.3	0.2	0.3	0.3	0.3
Max	1.5	1.5	0.8	1.3	1.3
Evaluated difference: baseline - treatment phase					
Mean	0.8	0.7	0.6	0.9	0.9
SD	0.64	0.46	0.68	0.69	0.69
Min	-0.6	0	-0.6	-0.6	-0.4
Median:	0.7	0.6	0.5	0.7	0.8
Max	2.6	1.8	1.8	2.6	2.6

aSS = acute Symptom Score (evaluated by the investigator)

*1113 patients have been included in the report; for 2 patients are no data for treatment evaluation available. Therefore for 111 patients only, endpoint analysis with all symptom and treatment data have been performed.

See appendix 13.1: SAR, Table: 6-25 to Table: 6-28, Table 6-30 and Table 6-31.

Result of comparison of mean acute Symptom Scores (treatment phase) against baseline

Table 23 shows the statistics for the comparison of the mean treatment phase aSS versus baseline aSS for all patients as well as for the different age groups.

Positive values represent an improvement respectively a reduction of symptoms.

Table 23: Change of aSS - Treatment aSS compared to Baseline (mean difference)

Statistics aSS	aSS by all patients, N=111	aSS by children aged 4-11, N=28	aSS by Youths, aged 12-17, N=14	aSS by Patients (≥ 12), N=83	aSS by adults (≥ 18), N=69
Mean Difference	0.84	0.727	0.637	0.879	0.928
95% CI	(0.72, 0.96)	(0.55, 0.91)	(0.24, 1.03)	(0.73, 1.03)	(0.76, 1.09)
SD	0.64	0.46	0.68	0.69	0.69
t-value	13.77	8.35	3.48	11.57	11.2
DF	110	27	13	82	68
p	< 0.0001	< 0.0001	0.0040	< 0.0001	< 0.0001

See appendix 13.1: SAR, Table: 6-29 to Table: 6-30.

Descriptive statistics for the difference aSS baseline minus aSS treatment phase are represented in Table 22.

An overview on all measured scores for secondary endpoint analysis is given in Table 24. Scores measured at baseline, during treatment phase and the evaluated difference between baseline and treatments scores are shown.

Table 24: Summary of mean QoLS, mean wMS, mean aSS compared to baseline

All Symptom Scores	All Patients N = 111*1	Children aged 4-11 N = 28	Youths aged 12-17 N = 14	Patients (≥ 12) N = 83	Adults (≥ 18) N = 69
Quality of Life Score (QoLS)					
Mean Baseline	9.4	7.1	8.7	10.2	10.5
Mean Evaluation phase	2.5	1.8	1.7	2.7	3
Mean difference Baseline - Evaluation Phase	6.9	5.3	7	7.5	7.6
P_Value	< 0.0001	< 0.0001	0.0002	< 0.0001	< 0.0001
Medication Score (wMS)					
Baseline	0.142	0.24	0.112	0.108	0.108
Mean Evaluation Phase	0.086	0.09	0.047	0.084	0.092
Mean difference Baseline - Evaluation Phase	0.056	0.15	0.065	0.024	0.016
p-Values	0.0960	0.0476	0.3064	0.5151	0.7142
Acute Symptom Score (aSS)					
Baseline	1.2	1	1	1.3	1.3
Mean Evaluation Phase	0.4	0.3	0.4	0.4	0.4
Mean difference Baseline - Evaluation Phase	0.8	0.7	0.6	0.9	0.9
p-value	< 0.0001	< 0.0001	0.0040	< 0.0001	< 0.0001

wQoLS = weekly Quality of Life Score, wMS = weekly Medication Score, aSS = acute Symptom Score

7.6.7 Quality of the used Measurement Instruments

The weekly symptom score, the quality of life score and the weekly medication score are based on commonly used instruments. In order to keep the burden on the patients as low as possible and to avoid keeping a diary, simplifications were made. For symptoms, questions were asked about the most severe expression and the number of days with the most severe expression. Questions about quality of life were treated in the same way. In the case of medications, questions were asked about the number of days a particular class of medication was taken. However, no assignment to individual days was made. As a result, the results are more "blurred" compared to a dedicated patient diary.

Cronbach's alpha was determined for the scores in order to check whether the instruments used met the usual requirements for the formation of scores. The weekly medication score was excluded from this, as the score is the selected maximum of a few items.

Cronbach's alpha is a measure of the internal consistency of the items that make up a score, i.e., how closely a group of items is related to each other. It is considered a measure of scale reliability. The resulting α -reliability coefficient ranges from 0 to 1. Acceptable values for alpha are between 0.70 and 0.95. Scores of questionnaires/scales with alpha coefficients $\geq .70$ can be used without hesitation for further analyses.

Table 25: Cronbach alphas for the used Outcome Measures

Measure	Cronbach Alpha
Weekly Symptom Score (wSS)	0.80
Acute Symptom Score (aSS)	0.83
Quality of Life Score (QoLS)	0.91

See appendix 13.1: SAR, Table: 8-1.

The Cronbach's-alphas of the outcome measure scores are good to very good (see Table 25).

The acute symptom score was collected according to standard. It can therefore be used to assess the validity of the weekly symptom score and the Quality of Life score. For this purpose, the correlations of the scores at baseline are calculated. High correlations are expected between the symptom scores and somewhat lower but still significant between the symptom scores and the Quality of Life score.

Table 26: Correlation of Scores at Baseline

	wSS	QoLS	aSS	wMS
wSS	1.00	0.64	0.71	-0.02
QoLS	0.64	1.00	0.59	0.01
aSS	0.71	0.59	1.00	-0.14
wMS	-0.02	0.01	-0.14	1.00

See appendix 13.1: SAR, Table: 8-2.

The correlation of wSS and aSS with $r = 0.71$ is high. This indicates that both measures capture similar constructs. The high correlations of the weekly and acute Symptom Scores with QoLS ($r = 0.64$ and respectively $r = 0.59$) can be interpreted as external construct validation of the QoLS. The Medication Score shows no or only small and statistically not significant correlations with the other scores. One reason is that in the investigated sample the usage of conventional medication is low. The strong skewed distribution of values reduces potential correlations.

The wSS as primary endpoint and the aSS and QoLS as secondary endpoints meet the expectations for reliability and validity.

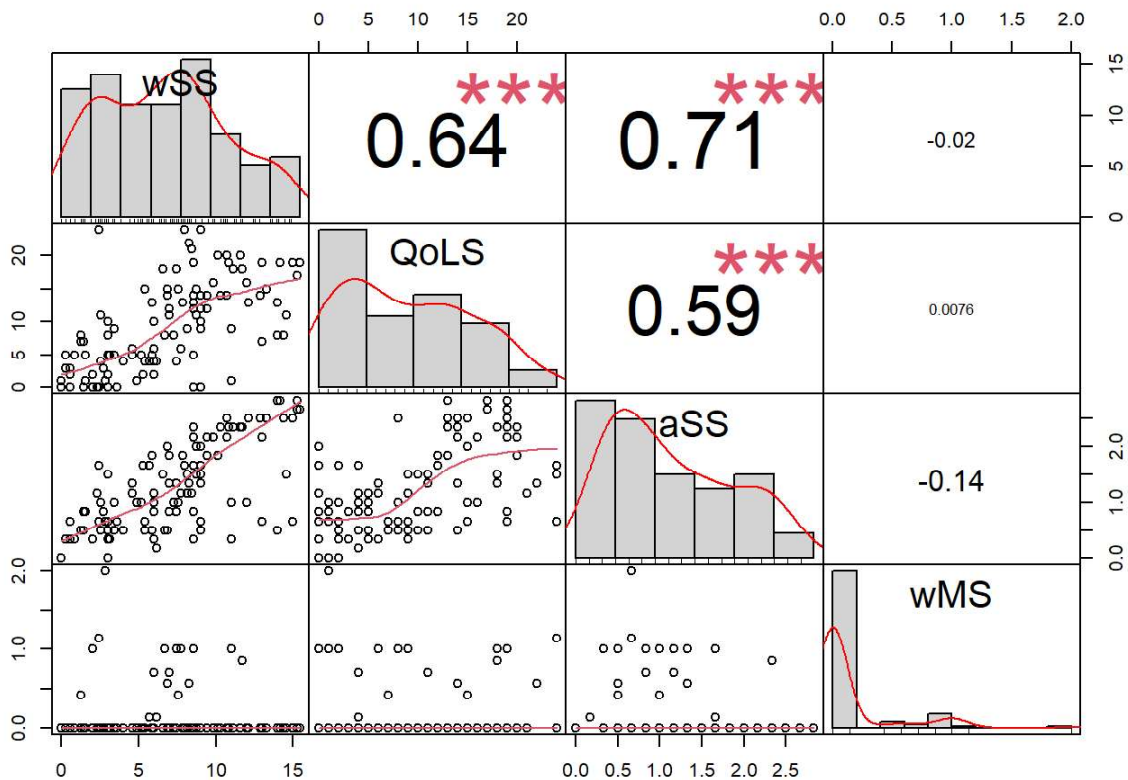


Figure 7: Correlations, Histograms and Scatterplots for Outcome Measures at Baseline

See appendix 13.1: SAR, section 9 for details.

The figure shows in compact form the most important information on the primary and secondary endpoints at the time of baseline. The upper right triangle shows the correlations between the scores. The three red asterisks mark highly significant (compared to a null correlation, $p \leq 0.001$) correlations. On the diagonal, the figures include the names of the scores and show the distribution of the variables (small to high values) as histograms and fitted density lines. The scores are not normally distributed but show an acceptable distribution except for the wMS. The highest bar in the histogram for wMS represents no medication. The lower triangle contains the bivariate distribution of scores as scatter plots with fitted regression lines (Loess). Horizontal and vertical lines to the corresponding diagonals show the variables that make up the bivariate measures.

7.6.8 Sensitivity Analysis

Sensitivity analyses examine whether there are causes or explanations other than the treatment for the observed effect. Due to the distribution of the measured values (see Figure: 7), it can be excluded that extreme values are responsible for the result. Since the success does not depend on the duration of the treatment, e.g. an optional stopping, i.e. a therapist discontinues the treatment if a patient shows particularly good results, can be excluded. Thus, determining the mean symptom score over the entire evaluation period as a method to avoid optional stopping of the treatment by the investigator has proven effective. The observed effect also remains stable across different subgroup formations. The only striking feature is that the study sites differ considerably in terms of the mean severity of symptoms with which patients were included into the study. However, patients with lower symptomatology naturally have less room to improve their symptoms (bottom effect). Overall, the observed effect proves to be robust and therefore cannot simply be explained away. Following figures are exemplary.

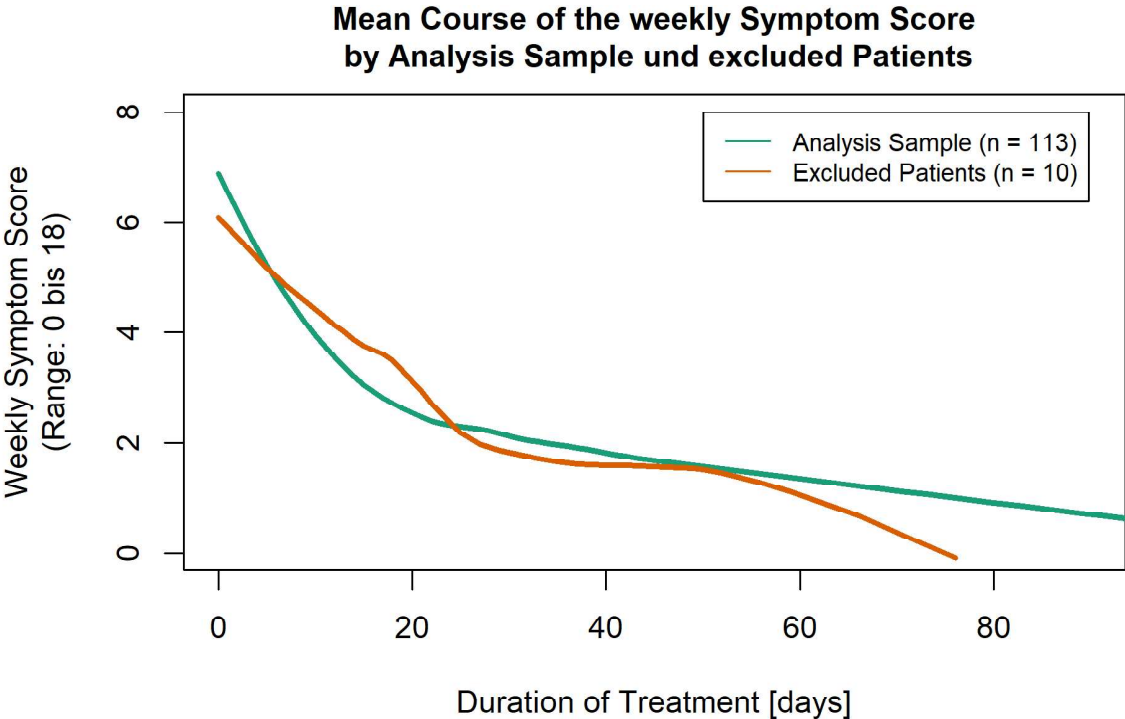


Figure: 7 - 1: Mean Course of the weekly Symptom Score by Analysis Sample und excluded Patients

The graph is cut off after 90 days. The mean course was determined by locally estimated scatterplot smoothing.

Boxplot - Change of weekly Symptom Score for Analysis Sample und excluded Patients

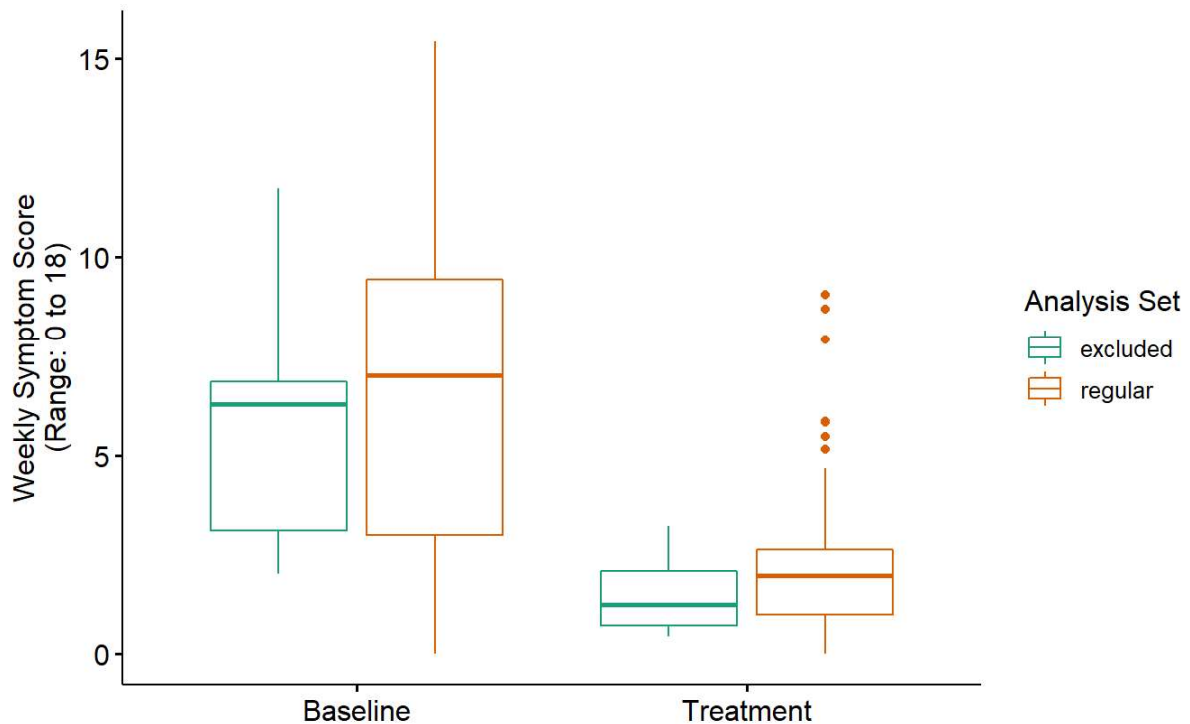


Figure: 7 - 2: Weekly Symptom Score for the Analysis Sample an excluded Patients - Boxplot

A boxplot is a standardized way of displaying the distribution of data based on a five number summary ("minimum", first quartile (Q1), median, third quartile (Q3), and "maximum"). The box shows the range for middle 50% of scores. Single points represent outliers.

7.6.9 Safety Endpoint

Adverse Events (AEs) have been evaluated in 6/113 patients (5.3 %). No major complications have been reported, the intensity of all events was mild to moderate. All patients recovered from their AEs. The patient who experienced AE-2 decided together with the physician to discontinued the treatment during consultation.

No Serious Adverse Event (SADE) has been reported.

A total of 6 AEs occurred in 113 patients. None of these AEs were classified as serious. Thus, in summary, it can be stated from the current point of view that the risk-benefit assessment has not been changed.

Details see Table 27 and 28

Table 27: Overview of patients with all adverse events (AE)

AE No	Pat- No	Sex	Age	Intensity of the AE	AE Resolution	AE Related to treatment	AE Related to device
AE-1	01-06	Female	41	Moderate	Yes	Yes	No
AE-2	02-05	Male	30	Moderate	Ongoing	No	No
AE-3	09-07	Female	33	Moderate	Yes	Yes	No
AE-4	10-05	Female	33	Mild	Yes	uncertain	uncertain
AE-5	10-08	Female	77	Mild	Yes	uncertain	uncertain
AE-6	10-09	Female	65	Mild	Yes	uncertain	No

See appendix 13.1: SAR, Table: 11-1

Table 28: Overview of the occurred adverse events (AEs)

AE No	Pat No	AE Diagnosis	Short description of the AE
AE-1	01-06	Worsening of rhino-conjunctivitis	severe initial reaction with itchy, runny and congested nose, sneezing, reddened and watery eyes with considerable impairment of general condition for 2 days, then better
AE-2	02-05	Nausea, stomach acidity	In the course of time, the patient complained more and more often about overacidification of the stomach and nausea than about allergy symptoms in the sense of watery eyes or a blocked nose or similar.
AE-3	09-07	Migraine	Migraine with sweating, dizziness
AE-4	10-05	Recurrent Diarrhea	increased bowel movements and very much thirst. Slight headache, less appetite
AE-5	10-08	Fissures right eye, upper lip due to dry skin	Slight restlessness, one night not slept, eye right and upper lip small skin tear with dry skin with slight redness
AE-6	10-09	Initial aggravation	Increase in sneezing suspected due to therapy

See appendix 13.1: SAR, Table: 11-2

8 Discussion and overall Conclusions

8.0 Safety or Performance Results and any other Endpoints

This prospective, multicenter, observational study were designed to investigate the treatment of mild to moderate rhino-conjunctivitis with the bioresonance therapy and to collect performance and safety data of the BIOCOM optima device.

The primary endpoint was to evaluate the mean weekly Symptom Score, captured after the first allergy treatment session until follow-up visit within two weeks after the last allergy treatment in the study and compared to baseline.

The primary safety endpoint was the collection and assessment of adverse device effects (ADE), device and/or procedure related and serious adverse device effects (SADE), device and/or procedure related

The used measures for primary and secondary endpoints met the common criteria for reliability and validity.

8.0.1 Performance Results – Primary Endpoint Analysis

The mean weekly symptom scores (mean wSS) measured after the first allergy treatment session compared to the baseline symptom score is the primary endpoint for performance in this study.

(Table 15 Baseline wSS and mean wSS, section 7.6).

The lower the wSS-value the lesser was the patient's burden with symptoms. See Table 16 in section 7.6 for overview on results (baseline wSS, mean wSS and the evaluated change of wSS / the mean wSS at allergy treatment compared to baseline).

One hundred eleven patients provided primary outcome data for this analysis. The mean weekly symptom score (wSS) decreased from 76.97.6 to 2.12.52. points averaged on the visits, reflecting a clinically and statistically significant improvement ($p < 0.0001$, two-sided dependent t-test and 95% CI; 4.145, 5.6156). The absolute change in score, which is 4.9, is clearly above the minimally important difference (MID; 21.10 points, calculated from data) in wSS values and, therefore, represents a clinically significant difference for all patients. See also Table 17, Change of wSS – Treatment wSS compared to Baseline wSS, for all details and effects on the different population groups.

In addition, the results for all age sub groups (Children from 4 to 11 years, N = 3028; Youths from 12 to 17 years, N = 15 14 and adults (≥ 18 years, N = 7369) are independent statistically and clinically significant with mean reductions of 4.274.53, 4.764.57 and 5.145.04 respective.

8.0.2 Performance Results – Secondary Endpoint Analysis

Secondary performance endpoints are the Quality of Life Score (QoLS), the mean weekly medication score (wMS), both evaluated by a patient questionnaire, and the mean acute symptom score (aSS), evaluated by the investigator. All scores are captured at the first treatment visit as baseline and from all treatment sessions after the first allergy treatment session until the last treatment session, and, if applicable, follow up until two weeks after last treatment session for treatment evaluation.

The Quality of Life Score and the acute Symptom Score show also highly statistically significant improvements of the patients compared to baseline for the whole sample as well as all age sub groups. Only the weekly Medication Score shows no change on a sample with general low level of the use of conventional medications for symptom reduction.

An overview/summary on all measured scores for secondary endpoint analysis is given in section 7.7. Scores measured at baseline, during treatment and the evaluated change of scores between baseline and treatments are shown in Table 24, Summary of mean QoLS, mean wMS, mean aSS and treatment scores compared to baseline.

8.0.3 Safety Results

All AEs collected until the cut-off date have been evaluated.

No SADE has been reported. For details see table 26 and 27 in section 7.7.

AEs have been evaluated in 6/113 patients (5.3 %). No major complications have been reported and the intensity of all events was mild to moderate.

8.1 Assessment of Risks and Benefits until Cut-off Date

No major complications have been reported, the intensity of all events was mild to moderate

The risk benefit assessment has not been changed.

Scoring of symptoms and allergy rescue medication use are key outcomes for clinical trials with allergen immunotherapy. The definitions and calculations of scoring vary widely from trial to trial. Although allergy organizations and government agencies considered standardizing scoring methods for allergen immunotherapy trials, other clinical and methodological differences in trial characteristics and design need to be taken into account when considering efficacy. Thus, symptom, medication, or combined scores among trials cannot be compared without taking the methods of scoring and other trial differences into account (Calderon 2014).

Measurement of allergy symptoms is a standard endpoint in allergen immunotherapy trials. The accepted method of scoring allergy symptoms is the daily symptom score (dSS). Food and Drug Administration (FDA), European Medicines Agency (EMA), and World Allergy Organization (WAO) guidelines all recommend a dSS using the four symptoms of nasal congestion, rhinorrhea, sneezing, and itchy nose. In addition, the WAO recommends evaluating at least one ocular symptom, and the EMA recommends specifically evaluating the two ocular symptoms of itching/grittiness/redness and tearing.

The weekly symptom score (wSS) was chosen in this study in order to keep the burden for the patient low and due to the fact that this was an observational study without any study specific procedures. For collection of the daily symptom score (dSS) it would be mandatory for the patient to keep a diary about daily symptoms. Also, the use of a daily combined symptom and medication score (DCSMS) as the primary efficacy endpoint has been discarded due to the fact that only patients with mild to moderate symptoms are treated. Patients with mild to moderate symptoms are less likely to take standard drugs and therefore a visible effect in reduction of medication might not be expected. However, the weekly medication score (wMS) was chosen as secondary endpoint, due to the fact that the before mentioned assumption might be wrong.

One key difference among trial designs that has affected interpretation of efficacy is the use of varying methods for scoring and analyzing symptom and rescue medication use. Therefore, a comparison to other studies, e.g. allergy immunotherapy studies, is not possible.

8.2 Any specific Benefits or special Precautions required for individual Subjects or Groups considered to be at Risk

N/A

8.3 Any Implications for the Conduct of future clinical Investigations

N/A

8.4 Limitations of the clinical Investigation

Limitations of this study are those of a non-interventional prospective, uncontrolled study in the real-life setting, like unpredictable bias, confusion bias and selection bias. In order to minimize a potential investigator and selection bias of the study, sites distributed all over Germany were involved.

The study results show a significant effect. However, it must be critically noted that with the design of this study, namely single-arm with an intraindividual comparison of symptoms before and after therapy, it cannot be excluded that there are other causes for the improvement of the symptoms of the disease that could be observed in the study, such as the natural course of the disease, influence of the care within the study, expectation of the patient when using a special treatment method. Thus, with this study, the placebo effect cannot be excluded, which means that the improvement of symptoms would have occurred even if a non-functioning bioresonance device had been used.

8.5 Overall Conclusion

The result of this study showed that the therapy of mild to moderate rhino-conjunctivitis with the BICOM optima device leads to a significant improvement of symptoms and quality of life. The short-term treatment efficacy and clinical benefit to the patient while they are receiving BRT could be shown.

In addition, the BICOM optima device is very safe; no serious adverse effects occurred during the course of the study.

An assessment of the long-term effect is not possible within the scope of this study. Likewise, as mentioned under 8.5, the placebo effect cannot be excluded as a possible cause for the good results. Therefore, it would make sense to have further studies follow that also investigate the long-term efficacy and clinical benefit.