Clinical Study Report

Final Report (period: 25.01.2021 –10.01.2022)

Version: 1.1

<table>
<tr><td colspan="4">Title of the study: Prospective, 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 patients with allergic rhino-conjunctivitis.</td></tr>
<tr><td colspan="2">Sponsor / Sponsor's Representative:
Regumed, Regulative Medizintechnik GmbH, Robert-Koch-Str. 1 a, 82152 Planegg</td><td>CIP Identification:
CIP_ARC003en_BICOM optima PMCF Study_V2.0, Version: 2.0, dated 14.01.2021</td><td>Date of final report: 06.07.2022
Author: Dr. Claudia Marx</td></tr>
<tr><td colspan="2">Study Centre:
9 study sites in Germany, 8 contributed patients.</td><td colspan="2">Study Period
Date first patient enrolled: 25.01.2021
Date last patient enrolled: 25.10.2021
LPLV: 10.01.2022</td></tr>
<tr><td colspan="2">Registration:
DRKS00024523</td><td colspan="2">Coordinating Principal Investigator:
Dr. med. Jürgen Hennecke, Trierer Str. 333, D-52078 Aachen</td></tr>
<tr><td colspan="2">Phase of development:
Post-market; device is used according to the IFU</td><td colspan="2">Investigational Device:
BICOM optima/BICOM optima Mobil</td></tr>
<tr><td colspan="2">Patients:
Planned: 132 (32 children from 4 to 11 years, 100 patients from 12 years)
analyzed 111 patients</td><td colspan="2">Patient Population: Patients with age from 4 years diagnosed with symptomatic allergic rhino-conjunctivitis.</td></tr>
<tr><td colspan="4">CRO:
CERES GmbH evaluation & research, Brombacher Str. 85, 79539 Lörrach, Germany, Fax: 07621 | 167 333 20
Responsibilities:</td></tr>
<tr><td>Biostatistics:
Emil Boller
☎: 07621 | 167 333 33</td><td>Study coordination:
Dr. Claudia Marx
☎: 07621 | 167 333 70</td><td>Monitoring:
Dr. Angelika Doerner
☎: 07621 | 167 333 83</td><td>Data Management:
Inka Mueller-Velte
☎: 07621 | 167 333 34</td></tr>
</table>

Proprietary and Confidential

Version	Document ID	Date of release	Reason for change
1.0	CSR_ARC003en_BICOM_Clinical Study Final Report_V1.0	06.07.2022	Initial version
1.1	CSR_ARC003en_BICOM_Clinical Study Final Report_V1.1	14.07.2022	Minor editorial changes

This study was conducted in accordance with ISO 14155 that ensured adherence to Good Clinical Practices and protection of the subjects, as required by the directives in operation at the time.

1. General

This clinical study report describes the design, execution and statistical analysis of the BICOM optima/PMCF study. It is the final report, covering the period 25.01.2021 –10.01.2022 (LPLV). This final Clinical Study Report is based on the final monitored data of the study after database look.

2. Signature Page Sponsor and Coordinating Investigator

This Clinical Study Report was subject to a critical review and has been approved by the appropriate review committee of Regumed – Regulative Medizintechnik GmbH as well as the Coordinating Investigator.

The contained information is consistent with:

- The current risk/benefit evaluation of the device preparation;
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki in its current version;
- Good clinical practice guidelines as applicable for medical devices (ISO 14155, current version).

I have read this report and confirm with my signature that to the best of my knowledge it accurately describes the conduct and results of the study

Sponsor: Regumed – Regulative Medizintechnik GmbH	
Plaweg, 18.07.2022 Place/Date	R. Wollenzin Reiko Wollenzin
Coordinating Investigator	
Aachen 18.7.22 Place/Date	J. Hennecke Dr. med. Jürgen Hennecke

3. Signature Page Author and Review of the Report

CERES Clinical evaluation and research GmbH	
Author	
Place/Date	Dr. med. Claudia Marx
Review	
Place/Date	Emil Boller

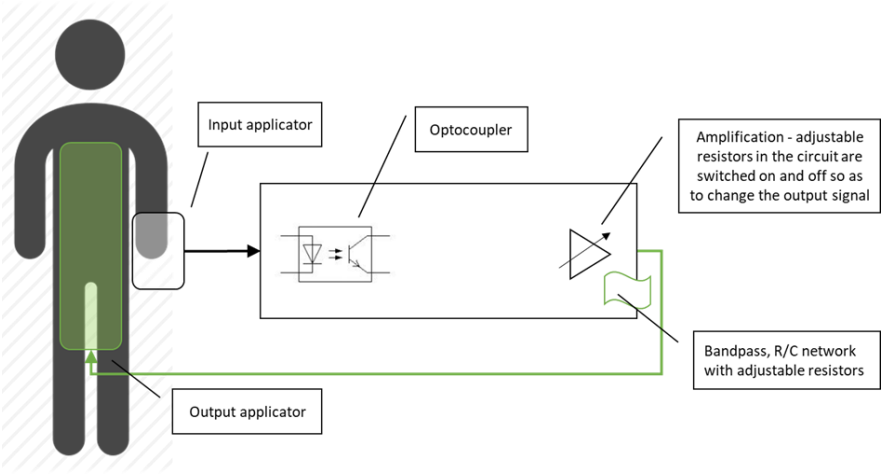
Table of content

4 Summary

Study Title	Prospective, 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 patients with allergic rhino-conjunctivitis.
Final Report	Covered period: 25.01.2021 -10.01.2022
Registration	DRKS00024523
Sponsor	Regumed Regulative Medizintechnik GmbH Robert-Koch-Str. 1 a 82152 Planegg Germany Contact: Reiko Wollenzin Tel: +49 (0) 174 9080940 e-mail: r.wollenzin@regumed.de
Investigator(s) and Study Site(s)	**Coordinating Principal Investigator:** Dr. med. Jürgen Hennecke Trierer Str. 333 D-52078 Aachen Germany Tel.: +49 (0) 241 - 56 20 15 E-mail: drhennecke.ac@t-online.de **Other Principal Investigators in Germany:** Marie Christin Etti Dr.med. Susanne von Ohlen Dr.med. Karin Bösler Dr. med. Tobias Schipper Dr. Julia Berg Dr. med. Uta Schmieden-Lindner Dr. med Richard Baustädter Details see section 11.1.
Other Institutions	**CRO:** CERES GmbH evaluation & research

	Brombacher Str. 85 79539 Lörrach, Germany
Publication(s)	N/A
Study Data Details	Date first patient enrolled: 25.01.2021 Date last patient enrolled: 25.10.2021
Clinical development phase	Post-market; device is used according to the IFU
Study Design	A multi-center, single-arm, prospective, open-label, observational post-market clinical follow-up study using BICOM optima B32/ B34/ Mobil BM34 device for bioresonance treatment in patients with symptomatic allergic rhino-conjunctivitis. Patients with mild to moderate allergic rhino-conjunctivitis will be treated according to the clinical routine and in accordance with the current IFU.
Introduction	**Bioresonance** is a medical technique that belongs to the field of complementary medicine. Its intended purpose is to stimulate the self-regenerating system of the human body and is working with biological magnetic fields. The BICOM systems are recommended for the treatment of **mild to moderate allergies** and **allergy-related diseases or complications**, but focussing on **allergic rhino-conjunctivitis**. Allergic diseases represent a pathologic information carried by a wave pattern in an otherwise harmonic electromagnetic field of a living organism. Bioresonance is used for the treatment of mild to moderate allergies and allergy-associated diseases in adults and children by applying inverse electromagnetic wave patterns of the allergen (Ai mode of a bioresonance device). During the physical inversion of an arbitrary oscillation, the characteristic wave pattern remains unchanged. If the inverted electromagnetic wave pattern coming from the device is now confronted with the original pattern in the patient, the inverse oscillation leads to a reduction of the original pattern (Ref. in CER: Schumacher, 1990). Successful allergy therapy could be demonstrated by several clinical studies investigating performance and safety of BRM devices in allergic rhinitis and allergic conjunctivitis. In these prospective and retrospective, controlled (Ref. in CER: Huang 2005) and non-controlled studies (Ref. in CER: Schuhmacher 1998, Wang 2006, Yuan 2005, Yuan), a sustainable treatment success of BRM has been shown. The number of BRM sessions depends on the severity of the allergy and generally ranges between 3 – 20 sessions at weekly intervals. Results from clinical trials demonstrate that BRM might effectively reduce allergic

	symptoms and even sustainably cure allergies in as less as 3 – 20 therapy sessions. "Curing" was defined as no allergic symptoms and/or no recurrence of symptoms have been reported within follow-up of six months (Ref. in CER: Yuan, 2005). Reduction or even abolishment of the need for systemic and non-systemic drugs that suppress allergic symptoms has been reported (CER: 20200804-799-BCM-Clinical Evaluation-Rev B.00, dated 19.11.2020, see chapter 6.1.1.3). Physiologic damages caused by the delivery of high energies are precluded as bioresonance devices do not transfer high energies to the human body. Relevant adverse effects or BRM include the temporary aggravation of the treated symptoms after the start of the therapy. This first deterioration has been observed and reported by many physicians and therapists irrespective of the bioresonance device used. These symptoms are considered desirable as they are an indicator for the activation of the immune system and must not be eliminated (except in case of emergency) but may be mitigated by drug administration. The seriousness of these first reactions depends on the severity and characteristics of the treated disease (Ref. in CER: Schumacher, 1990). No severe side effects have been reported (Ref. in CER: Yang et al., 2004). Advantages of bioresonance therapy are the minimisation or even abolishment of the need for systemic and non-systemic drugs that suppress allergic symptoms which come along with several known side effects, e.g. drowsiness, nausea and (very rare) idiosyncratic hypersensitivity reactions.
Objectives **(Primary Objectives and endpoints)**	Objective of the PMCF-study is to assess performance and safety of the BICOM optima/BICOM optima Mobil for bioresonance therapy in patients with mild to moderate allergic rhino-conjunctivitis. The primary performance endpoint is: - Mean weekly Symptom Score (wSS): captured from the second allergy treatment session until 14 days after the last treatment in the study and compared to baseline. A maximum of 8 allergy treatments with the BICOM bioresonance therapy will be considered. The primary safety endpoints are: * - Adverse Device Effect (ADE), device and/or procedure related - Serious adverse device effects (SADE), device and/or procedure related **Adverse event will be collected from the first preparation treatment until the last allergy treatment followed by the one week follow up.*
Objectives	The secondary performance endpoints are:

(Secondary Objectives and endpoints)	- Mean Quality of Life Score as measured by a questionnaire - Mean need for medication - Mean acute symptom burden 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. Explorative endpoints are: - Symptoms, Quality of Life Score and need for medications in the preparation phase (treatments without allergy specific programs) compared to baseline.
Procedure and Measurement **Procedure and Measurement, continued**	With the BICOM systems, the patient is connected to the device by means of input applicators. The patient is galvanically isolated from the device by means of an optocoupler. The signals are transmitted via the input applicator to the device, processed according to the type of therapy being administered (see below) and then fed back to the patient via the output applicator. Signals are fed from and to the patient by analog transmission.  *(Intended Use – Annex II; General technical function)* The patients must be informed before they can be treated with the BICOM bioresonance therapy that they should not consume alcohol on the day of treatment. During the treatment the investigator pay attention if unpleasant feelings such as dizziness, nausea or head pressure occur during therapy or at the end of therapy. In the occurrence of this case the therapy should be stopped briefly until patient feels better. It is also important to ensure that the applicators of the device shall not be used directly on injured skin. ***Measurement:*** The patients will usually undergo up to 2 preparation sessions, at least 3 and a maximum of 8 BICOM bioresonance allergy treatment sessions with

treatment free intervals of one to two weeks. The duration of the allergy treatment period (treatment phase) will take from at least 3 up to a maximum of 13 weeks, adapted to the patient's response to the therapy. If a patient requires more than 8 allergy treatment sessions, the data collection for treatment is terminated with the 8th treatment session or after 15 weeks of treatment whatever comes first. All patients will get afterwards a one week follow up. Follow up data can be collected before the start of a BICOM treatment after end of treatment in the investigation.
Each BICOM bioresonance treatment session is divided into different parts that contain a selection of programs. The preparation treatment sessions usually are used to improve the responsiveness of the organism and to remove therapy blockages (See study schedule treatment session 1 and 2). They include programs for basic therapy, blockage-releasing programs and programs for cleansing and balancing of the body from an energetic viewpoint. From the third treatment session, blockage-releasing programs and programs for cleansing and balancing of the body and the specific allergy treatment programs and supporting symptom-related programs will be applied (See study schedule treatment session 3 up to 10).
Before every treatment session and one week follow up after the last allergy treatment relevant for study, the weekly symptom score (wSS), the medication score (MS), the Quality of Life questionnaire data and the actual symptoms (evaluated with the actual symptom score, aSS), estimated by the investigator, are collected.
The collected data represents always the status of the patient in the week before measurement with exception of the actual symptoms. This also applies, if more than a week has passed between two treatment sessions.

It is possible to include patients in the study who have already received bioresonance therapy in the past. These patients will not receive any pre-treatment.

ADE/SADE will be collected from the first preparation treatment until the last treatment within the study.

Study schedule:

	Visit 1 (optional)	Visit 2 (optional)	Visit 3 to Visit max 10, if applicable	EOS for each patient
	Preparation Treatment Session 1	Preparation Treatment Session 2	Allergy Treatment Session 3 up to Session 10	one week Follow up after the last allergy treatment
Informed consent [a)]	X			
Anamnesis [a)]	X			
Demographic data [a)]	X			
Symptom Score [a), b)]	X	X	X	X
Medication Score [a), b)]	X	X	X	X
Actual Symptom Score by investigator [a)]	X	X	X	X
Quality of Life Questionnaire [a), c)]	X	X	X	X
Energetic testing [d)]	X	X	X	
Basic treatment [e)]	X	X		
Blockage -releasing treatment [f)]	X	X	X	

	Elimination treatment [g] X X X Allergy treatment [h] X ADE/SADE Recording [i] X X X ** One week follow-up take place one week after the last allergy treatment session* ***Note:** Before each Treatment session, including the two "preparation treatment" which include basic treatment, blockage -releasing treatment and elimination treatment, the patient's symptom score, the actual symptom score by the investigator, the medication score, and the Quality of Life questionnaire are recorded.* ***a)** Patients who do not receive preparation-treatment will be enrolled in the study before start of the first allergy treatment.* ***b)** adapted according to Pfaar et. al Allergy. 2014 Jul;69(7):854-67; The strongest symptoms and their duration in days are recorded and the recording of medication, including the duration of medication in days; see also section 5.1.* ***c)** Quality of life questions are evaluated for the influence of the rhino-conjunctivitis on 7 topics with 5-point rating scales and 5 topics for children* ***d)** Energetic testing: According to the clinical routine.* ***e)** Selection of a basic therapy program or a sequence from this category by conductance value. The basic therapy sequencies should not be used as individual programs, but the selected sequence should be run through completely.* ***f)** Select one, max. 3 blockage-releasing therapy programs or a program sequence of this category after bioenergetic testing.* ***g)** Select one, max. 3 elimination programs or a program sequence of this category after bioenergetic testing* ***h)** Select programs from Category 4: Allergy therapy and supportive symptom-related programs or a program sequence from this category. If possible, the program sequencies should not be split up, but should be used completely. Please select max. 1 program sequence per session and, if necessary, an additional program or max. 4 individual programs.* ***i)** Adverse device effects (ADE) and serious adverse device effects (SADE) were recorded from the first treatment session. Be aware of that also, the first worsening of the treated symptoms and the duration of the first aggravation should be reported as (S)ADE.*
Patient Population:	Patients with age from 4 years diagnosed with allergic rhino-conjunctivitis caused by - pollen (e.g. tree, grass) - house dust mite (HDM) - animal hair allergy
Number of patients who participated in the study	**Planned number of subjects to be enrolled:** 132 (32 children from 4 to 11 years, 100 patients from 12 years) **Number of analysed patients within this report**: 113 patients have been included in the study. 111 patients have been analysed for primary endpoint. Details see section 7.2.
Medical condition or pathology studied	**Intended use and indication:** The BICOM systems belong to the complementary medicine and aim to activate and restore the body's own self-healing powers using the bioresonance therapy method. The BICOM systems are recommended for the treatment of mild to moderate allergic and allergy-related diseases or complications, but focussing on allergic rhino-conjunctivitis.

	Bioresonance therapy is a complementary medical practice in which it is proposed that low energy electromagnetic waves can be used to treat human illness. The BICOM system is recommended for use with adults and children aged 4 years and older. The device is a medical device (risk class IIa) for professional use. It was developed exclusively for use by trained, licensed doctors, state-approved naturopaths or trained medical professionals under their supervision. Allergic rhinitis (AR) is a chronic inflammatory disorder of the nasal mucosa caused by IgE-mediated early- and late-phase hypersensitivity responses. AR symptoms include rhinorrhea, nasal obstruction and blockage, nasal itching, and repetitive sneezing. It is also often accompanied by allergic conjunctivitis (ARC) with symptoms that can include itchy, red, watery, and/or swollen eyes. Because of the non–life-threatening nature of symptoms, AR and ARC have, in the past, been considered trivial diseases but are increasingly recognized as having a major effect on quality of life (QOL), emotional well-being, sleep, daily activities, and productivity when poorly controlled (Blaiss 2018; ARIA guideline 2016).
Investigational medical device (s) studied:	BICOM optima/BICOM optima Mobil: BICOM optima B32/ BICOM optima B34/ BICOM optima Mobil BM34 device
Investigational reference device (s) studied:	NA

SUMMARY CONCLUSIONS of the FINAL REPORT

This study investigates the treatment of mild to moderate rhino-conjunctivitis. The results of this final analyses, based on monitored data.

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. Cronbach's alpha was determined for the scores, evaluated in the questionnaires, 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 formed from too few items. Acceptable values for alpha are between 0.70 and 0.95. Scores of questionnaires/scales with alpha coefficients ≥ .70 can be used without hesitation for further analyses.

The quality of the methods used to record symptoms, acute symptoms and quality of life are very good. The weekly symptom score (wSS) has an internal consistency of .80 and the acute symptom score (aSS) of .83. The questionnaire used to assess quality of life (QOLS) has an internal consistency of .91 (Cronbach alpha).

PERFORMANCE RESULTS – Primary Endpoint Analysis
111 patients have been analyzed in this report (see also Table 12, section 7.6). The mean weekly symptom score (mean wSS) at allergy treatment phase 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 treatment session (allergy treatment or preparation treatment), is used as baseline. All measures after the first allergy treatment inclusive timely conducted follow-up visit data are then summarized in a mean weekly symptom score for estimating allergy treatment efficiency (Table 15 Baseline wSS and mean wSS, section 7.6).

The wSS was collected by patient questionnaires filled by the 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 5.1.1). 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 16 in section 7.6 for overview on results (baseline wSS, mean wSS and the evaluated difference of the mean wSS at allergy treatment phase compared to baseline).

One hundred eleven patients provided primary outcome data for this analysis. The mean weekly symptom score (wSS) decreased from 7 to 2.1 points averaged on the visits, after the first allergy treatment 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 minimally important difference (MID; 1.0 point estimated in CIP, and calculated from data 2 points = ½ SD) 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 = 28; Youths from 12 to 17 years, N = 14 and adults (≥ 18 years, N = 69) are independent statistically and clinically significant with mean reductions of 4.26, 4.76 and 5.14 respectively.

PERFORMANCE RESULTS – Secondary Endpoint Analysis

Secondary performance endpoints are the mean 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 the second visit 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.

An overview/summary on all measured scores for secondary endpoint analysis is given in section 7.6. 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.

SAFETY RESULTS

All AEs collected until LPLV have been evaluated.

No SADE has been reported. Details see in section 7.6.

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.

CONCLUSION

This report based on monitored data, covering the period 25.01.2021 - 10.01.2022. One hundred eleven patients provided primary outcome data for this analysis. 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 mean weekly symptom score (wSS) evaluated by a questionnaire 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) in wSS values and, therefore, represents a statistically and clinically significant difference for whole sample and also age groups. See also Table 17 for details and effects for the different population groups. The study data show that safety and performance of the devices in question could be demonstrated.

Date of the eReport:	05.07.2022
Eudamed Number, if applicable:	N/A

5 Introduction

5.0 Background

According to the Allergic Rhinitis and its Impact on Asthma (ARIA) - Guidelines, **Rhinitis** is defined as an inflammation of the lining of the nose and is characterized by nasal symptoms including anterior or posterior rhinorrhoea, sneezing, nasal blockage and/or itching of the nose. These symptoms occur during two or more consecutive days for more than 1 h on most days. **Allergic rhinitis** is clinically defined as a symptomatic disorder of the nose induced after allergen exposure by an IgE-mediated inflammation. Allergic rhinitis (AR) is the most common form of noninfectious rhinitis and is associated with an IgE-mediated immune response against allergens. It is often associated with ocular symptoms (allergic conjunctivitis, ARC) (ARIA guideline 2016). Approximately 50–60% of patients with allergic rhinitis have associated symptoms of allergic conjunctivitis (Corren 2017).

Classical symptoms of AR are nasal itching, sneezing, rhinorrhea, and nasal congestion. Ocular symptoms are also frequent; allergic rhino-conjunctivitis (ARC) is associated with itching and redness of the eyes and tearing. Other symptoms include itching of the palate, postnasal drip, and cough. AR is also frequently associated with asthma, which is found in 15% to 38% of patients with AR, and nasal symptoms are present in 6% to 85% patients with asthma. In addition, AR is a risk factor for asthma, and uncontrolled moderate-to-severe AR affects asthma control. Compared with other medical conditions, AR might not appear to be serious because it is not associated with severe morbidity and mortality. However, the burden and costs are substantial. Moreover, it is now recognized that AR comprises more than the classical symptoms of sneezing, rhinorrhoea and nasal obstruction. It is associated with impairments in how patients function in day-to-day life. AR reduces the quality of life of many patients, impairing sleep quality and cognitive function and causing irritability and fatigue. AR is associated with decreased school and work performance, especially during the peak pollen season. AR is a frequent reason for general practice office visits. Annual direct medical costs of AR are substantial, but indirect costs associated with lost work productivity are greater than those incurred by asthma (ARIA guideline 2016).

Chronic rhinitis is an increasingly common condition that is now recognized to have a major impact on human health. Persistent nasal dysfunction may have significant effects on physical and emotional functioning, which result in absences from school and work, reduced worker productivity, and impaired school performance. Appropriate treatment of AR improves symptoms, quality of life, and work and school performance. (Corren 2017, ARIA guideline 2016).

Although rhinitis can be treated effectively with a number of medications, both over-the-counter and prescription products, allergen immunotherapy (AIT) remains the only disease-modifying treatment capable of causing long-term improvement with respect to nasal symptoms and reduction in incident cases of asthma (Corren 2017).

Allergen-specific immunotherapy (AIT) is the practice of administering gradually increasing quantities of an allergen extract to an allergic subject to ameliorate the symptoms associated with the subsequent exposure to the causative allergen (ARIA guideline 2009).

The standard treatment algorithm for AR/ARC begins with allergen avoidance. Patients are encouraged to limit exposure to relevant allergens by taking precautionary measures, such as closing windows to prevent pollen entry, maintaining humidity < 40% in homes to prevent dust mite and mold growth, and/or using high-efficiency particular air (HEPA) filters to remove animal dander from the air (Ref. in CER: Hossenbaccus et al. 2020). The recommended causative treatments include allergen-specific immunotherapy infections (desensitization), grass pollen allergy vaccine tablets and acupuncture.

Administrations of antihistamine and corticosteroids are recommended as symptomatic treatment methods. (Clinical evaluation report (CER), 20200804-799-BCM-Clinical Evaluation-Rev B.00, dated 19.11.2020, see section 3.3)

Bioresonance is a medical technique that belongs to the field of complementary medicine. Its intended purpose is to stimulate the self-regenerating system of the human body and is working with biological magnetic fields. The BICOM systems are recommended for the treatment of mild to moderate allergies and allergy-related diseases or complications, but focussing on allergic rhino-conjunctivitis. Allergic diseases represent a pathologic information carried by a wave pattern in an otherwise harmonic electromagnetic field of a living organism. Bioresonance is used for the treatment of mild to moderate allergies and allergy-associated diseases in adults and children by applying inverse electromagnetic oscillation of the allergen (Ai mode of a bioresonance device). During the physical inversion of an arbitrary oscillation, the characteristic wave pattern remains unchanged. If the inverted electromagnetic wave pattern coming from the device is now confronted with the original pattern in the patient, the inverse oscillation leads to a reduction of the original pattern (Ref. in CER: Schumacher, 1990).

Successful allergy therapy could be demonstrated by several clinical studies investigating performance and safety of BRM devices in allergic rhinitis and allergic conjunctivitis. In these prospective and retrospective, controlled (Ref. in CER: Huang 2005) and non-controlled studies (Ref. in CER: Schuhmacher 1998, Wang 2006, Yuan 2005, Yuan), a sustainable treatment success of BRM has been shown.

The number of BRM sessions depends on the severity of the allergy and generally ranges between 3 – 20 sessions at weekly intervals. Results from clinical trials demonstrate that BRM might effectively reduce allergic symptoms and even sustainably cure allergies in as less as 3 – 20 therapy sessions. “Curing” was defined as no allergic symptoms and/or no recurrence of symptoms have been reported within follow-up of six months (Ref. in CER: Yuan, 2005). Reduction or even abolishment of the need for systemic and non-systemic drugs that suppress allergic symptoms has been reported (CER: 20200804-799-BCM-Clinical Evaluation-Rev B.00, dated 19.11.2020, see chapter 6.1.1.3).

Physiologic damages caused by the delivery of high energies are precluded as bioresonance devices do not transfer high energies to the human body. Relevant adverse effects or BRM include the temporary aggravation of the treated symptoms after the start of the therapy. This intitial deterioration has been observed and reported by many physicians and therapists irrespective of the bioresonance device used. These symptoms are considered desirable as they are an indicator for the activation of the immune system and must not be eliminated (except in case of emergency) but may be mitigated by drug administration. The seriousness of these first reactions depends on the severity and characteristics of the treated disease (Ref. in CER: Schumacher, 1990). No severe side effects have been reported (Ref. in CER: Yang et al., 2004).

Advantages of bioresonance therapy are the minimization or even abolishment of the need for systemic and non-systemic drugs that suppress allergic symptoms which come along with several known side effects, e.g. drowsiness, nausea and (very rare) idiosyncratic hypersensitivity reactions.

Review of current literature clearly demonstrates the clinical need of medical products for the treatment of allergic diseases which affects – according to two large studies (DEGS1 for adults and KiGGS for children and adolescents) – 8.6% of adults living in Germany with asthma, 14.8% with allergic rhino conjunctivitis, 3.5% with atopic dermatitis, 3.5% with urticaria, 8.1% with contact eczema, 4.7% with food allergies and 2.8% with insect venom allergies (lifetime prevalence). It can be said that nearly one third of adults in Germany have been diagnosed with at least one of the abovementioned allergies during their lifetime by a physician (Ref. in CER: Langen et al., 2013). For children, lifetime prevalence

of 6.0% for bronchial asthma, 11.0% for hay fever, 12.8% for neurodermatitis and 2.8% for allergic contact dermatitis were reported (Ref. in CER: Robert Koch Institut, 2018).

Conventional symptomatic treatment modalities of allergic diseases include administering of antihistamines, corticosteroids, leukotriene receptor antagonists and inhaled beta2-agonists.

The bioresonance method can be used to treat mild to moderate allergies and allergy-associated diseases by the activation and restoration of the body's self-regulatory ability. Compared to these other methods available in this medical field, the bioresonance method is outstanding due to its drug-free and noninvasive application. It is also more cost-effective considering the high costs for the healthcare system especially for immunotherapy. There are very few risks associated with bioresonance therapy and no severe adverse events have been reported since introduction of bioresonance devices on the market. Furthermore, several clinical studies show a good performance of BRM devices with sustainable treatment success (Ref. in CER: Schumacher 1998, Huang 2005, Wang 2006, Yuan 2005, Yuan). Advantages of bioresonance therapy are the minimisation or even abolishment of the need for systemic and non-systemic drugs that suppress allergic symptoms which come along with several known side effects, e.g. antihistamines which may cause drowsiness, nausea and (very rare) idiosyncratic hypersensitivity reactions (Ref. in CER: Randall et al., 2018) or corticosteroids which may cause sore mouth, cough (Ref. in CER: US Department of Health and Human Services, 2007), and topical side effects, epistaxis etc. (Ref. in CER: Seidman 2015).

Compared with allergen-specific immunotherapy, bioresonance therapy requires less therapy sessions: The number of BRM sessions depends on the severity of the allergy and generally ranges between 3 – 20 sessions at weekly intervals (Ref. in CER: Yuan, 2005). Allergen-specific immunotherapy, by contrast, is a long-lasting procedure and involves receiving doses with increasing amounts of the allergens about one to two times per week, for a period of three to six months. Afterwards, maintenance doses are injected with longer periods of time between treatments, ranging from two to four weeks, in generally for three to five years (Burks et al., 2013). Further, by contrast to allergen specific immunotherapy, bioresonance therapy comprises fewer risks and side effects, and does not comprise the risk of systemic adverse reactions and anaphylaxis. Conventional immunotherapy (subcutaneous (SCIT) and sublingual route (SLIT)of application) techniques have, been beleaguered by significant rates of adverse reactions, raising concerns over safety and limiting its widespread use in the general population (Ref. in CER: Rajakulendran 2018). Due to the long duration and adverse reactions, only a minority of patients decides to undergo allergen-specific immunotherapy (Ref. in CER: Scheiblhofer 2018).

In conclusion, BRM is a complementary medicine approach which provides several benefits compared to other available causative and symptomatic treatment methods and is used for the treatment of allergies and allergy-associated diseases since several decades.

Crucial for the success of a treatment is a good education of the physician or alternative practitioner. Therefore, usage of the BICOM optima device is restricted to medical professionals.

5.1 Definition of Endpoints and Clinical Outcomes

This is a multi-center, single-arm, prospective, open-label, observational post-market clinical follow-up study using BICOM optima B32/ B34/ Mobil BM34 device for bioresonance treatment in patients with allergic rhino-conjunctivitis. Patients with mild to moderate allergic rhino-conjunctivitis are treated according to the clinical routine and in accordance with the current IFU.

Currently, allergen immunotherapy (AIT) remains the only disease-modifying treatment capable of causing long-term improvement with respect to nasal symptoms and reduction in incident cases of asthma (Corren 2017). In clinical trials, the efficacy of AIT is typically measured by evaluating the effect of treatment on symptom severity and allergy rescue medication use. Symptom and medication use are key outcomes for assessing the efficacy of AIT (Calderon 2014).

In 2008, the European Medicines Agency (EMA) provided guidance on AIT clinical trial design, suggesting primary and secondary endpoints as well as other trial design recommendations. Professional medical societies have also contributed recommendations for efficacy endpoints. According to these guidelines, an accepted demonstration of efficacy in allergic rhinitis with/without conjunctivitis (AR/ARC) is based on alleviation of symptoms as measured by subject symptom score and use of rescue medication. Thus, the efficacy endpoints chosen include daily symptom score (DSS) and daily medication score (DMS). Most notably, the EMA and professional medical societies agree on the use of a daily combined symptom and medication score (DCSMS) as the primary efficacy endpoint for AIT trials. However, several methods have been used to calculate DCSMS; therefore, methods for calculating this endpoint are still not standardized (Nelson 2017).

To begin to address this issue, a European Academy of Allergy and Clinical Immunology (EAACI) task force (TF) published recommendations on methods of assessing DSS, DMS, and DCSMS. The position paper of the EAACI described the advantages and disadvantages of commonly used AIT clinical trial outcomes, and provided consensus recommendations for the definitions and scoring of clinical measures of efficacy (clinical outcomes) (Pfaar 2014).

As primary outcome, the EAACI recommended a homogeneous combined symptom and medication score (CSMS) as a simple and standardized method that balances both symptoms and the need for antiallergic medication in an equally weighted manner (Pfaar 2014).

5.1.1 Mean weekly Symptom Score

Individual ARC patients are affected by nasal and ocular symptoms.

The most frequently used primary efficacy criterion for symptom severity is the mean total rhino-conjunctivitis symptom score (RCSS) over a specified period related to the exposure of allergens (e.g. the entire pollen season to be precisely defined for grass pollen AIT and a selected period of HDM exposure or direct exposure to animals). The mean total RCSS is based on the daily evaluation of six to eight individual rhinitis and conjunctivitis symptoms, usually on a four-point scale (starting with 0=no complaints and 3=severe symptoms).

The advantages are:

- There exists a well-defined terminology for two symptoms in the eye (ocular itching/grittiness/redness and ocular tearing) and for four symptoms in the nose (nasal itching, sneezing, rhinorrhea (runny nose) and nasal obstruction (congested nose).
- The 0–3 symptom score accepted by the FDA and the EMA is simple and easy to use. The score is: **0** = no symptoms (or signs); **1** = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated); **2** = moderate symptoms (definite awareness of sign/symptom that is

bothersome but tolerable); **3** = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping).

For this study, the primary efficacy criterion for symptom severity was the difference between the symptom score at baseline and the mean weekly symptom score (wSS), captured from the second allergy treatment session until one week after the last allergy treatment in the study. The weekly symptom score is measured by a symptom questionnaire, filled out by the patient (see Table 1). Patient's weekly symptom score (wSS) is captured from the second allergy treatment session until one week after the last allergy treatment in the study and the mean wSS is compared to baseline. A maximum of 8 allergy treatments with the BICOM bioresonance therapy are considered.

The weekly symptom score (wSS) was chosen in order to keep the burden for the patient low. 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. Nevertheless, the weekly medication score (wMS) was chosen as a secondary endpoint.

The minimally important difference (MID) has been defined as the smallest improvement considered worthwhile by a patient. Results of a study by Devillier et al (2014) suggest that the MID for the improvement of a rhino-conjunctivitis total symptom score in grass-pollen-induced allergic rhinitis is at least 1 unit in children, in adolescents and in adults. This value appears to be the smallest meaningful change in the total symptom score. The use of the MID has been adapted to this PMCF study. Treatment is regarded efficient, if an improvement ≥1 point was observed.

Patients suffering from mild to moderate allergic rhinitis are affected by nasal and ocular symptoms. With the use of the symptoms score (SS) the therapist evaluates the patient's symptoms based on a survey of symptoms before the first allergy therapy starts and in the subsequent treatment weeks before each BICOM bioresonance treatment and one week follow up.

Nasal symptoms are in accordance to Pfaar et al (2014) itchy nose, sneezing, runny nose, congested nose. The conjunctival symptoms are itching/reddened eyes and watery eyes. The severity of the symptoms is classified as follows: **0** = no complaints; **1** = slight complaints (clearly present but hardly noticed); **2** = moderate Complaints (annoying but bearable); **3** = severe complaints (difficult to bear, disturbing daytime activities/sleep). The results are summarized in the (total) weekly Symptom Score (wSS). Patients will be asked in questionnaires for assessment of the 4 nasal symptoms (itchy nose, sneezing, runny nose, congested nose) and 2 conjunctival symptoms (itching/reddened eyes, watery eyes) scoring it with 0, 1, 2 or 3.

Table 1: Adapted Symptom Score according to Pfaar et al 2014

Symptom Score (score 0 – 3)		
nasal symptoms	itchy nose	max (0–3*) x n days
	sneezing	max (0–3*) x n days
	runny nose	max (0–3*) x n days
	congested nose	max (0–3*) x n days
conjunctival symptoms	itching/reddened eyes	max (0–3*) x n days
	watery eyes	max (0–3*) x n days
(Total) weekly Symptom Score, TWSS = sum of the numbers/7		∑ / 7
*0 = no complaints; 1 = slight complaints (clearly present but hardly noticed); 2 = moderate Complaints (annoying but bearable); 3 = severe complaints (difficult to bear, disturbing daytime activities/sleep) n = number of days with the greatest severity of allergy symptoms (between 1 to 7 days, estimated by the patient). If "no complaints", the value must be 7; otherwise it is between 1 to 7.		

As mentioned before, the primary endpoint in this study is calculated as the mean weekly symptom score (mean wSS) at allergy treatment compared to baseline.

The primary study objective for safety was the collection of device and/or procedure related (serious) adverse device effects. Adverse device effects (ADE) are collected from the first allergy bioresonance treatment or preparation treatment, if applicable, until the last allergy treatment within the study.

For ADE, SADE and/or procedure related assessment, patients have been asked during their visits for BICOM bioresonance treatment, if they had any adverse events (device and/or procedure related).

The secondary study objectives were the evaluation of changes of quality of life, acute symptoms and the need for medication in treatment phase follow up compared to baseline.:

- Mean Quality of Life Score **(QoLS)** as measured by a questionnaire
- Mean need for medication (measured as mean weekly medication score, **wMS**)
- Mean acute symptom burden, measured as acute Symptom Score (mean **aSS**)

All parameters measured at start of any visit by questionnaire or investigator. Measure at the first visit serves as baseline. Measures captured after the first allergy treatment visit until end of treatment and, if applicable one follow-up visit within two weeks after the last treatment session are used for treatment evaluation.

5.1.2 Quality of Life Score (QoLS)

Allergic rhino-conjunctivitis (AR) is a highly prevalent condition that can impair also quality of life (QoL). In clinical trials, symptom severity is evaluated using patient-reported outcomes such as a total symptom score or a disease-specific quality of life sore (QoLS). The effects of allergic rhinitis on health-related Quality of Life (QoL) extend to learning, sleep, vitality / alertness, perception of general health, cognitive and emotional functioning, and psychomotor performance. All these possible limitations in patients' day to day can have considerable negative effects on the person's performance both at work or school, and at home, having a direct and indirect economic impact on society (Cuesta-Herranz 2019).

A secondary objective of this study was to evaluate the changes in health-related QoL in patients with AR, assessed by a Quality of Life Questionnaire, QoLQ, 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 second allergy treatment session until one week after the last allergy treatment 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.

5.1.3 Medication Scores (MS)

Allergy treatment reduces symptoms as well as the use of medication in the allergic individual. Because the use of rescue medication has an impact on symptom severity/scores, it must be recorded on a daily basis as the medication score (MS). The MS is an indicator of allergy treatment efficacy (Pfarr 2014). Depending on the class and route of medication one to three points are given.

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

The need for medication was evaluated with the medication score (adapted to Pfaar 2014). In this study, the MS was regarded as an indicator of BRT efficacy (see Table 2).

Initially, the use of a daily combined symptom and medication score (DCSMS) as further secondary efficacy endpoint has been discussed. It was 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 clearly expected. However, the weekly medication score (wMS) was chosen as secondary endpoint, due to the fact that the before mentioned assumption might be wrong.

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 was defined as the (Total) weekly Medication Score (wMS).

Table 2: Adapted Medication Score according to Pfaar et al 2014

Medication Score (0 – 3; max. score is 3)*	
Oral and/or topical (eyes, nose) non-sedative H1 antihistamines	1 x n days
Intranasal glucocorticoids with/without H1 antihistamines	or 2 x n days
Oral glucocorticoids with/without intranasal glucocorticoids, with/without H1 antihistamines	or 3 x n days
(Total) weekly Medication Score (wMS)=max of the numbers / 7	Max. value / 7

*Score is determined by the applied allergy medication

5.1.4 Acute Symptom Score (aSS)

In addition, an acute symptom (aSS) score is evaluated by the investigator directly at the visit of the patient as one of the secondary endpoints for efficacy. Before every treatment session and one follow up after the last treatment relevant for study, the actual symptoms estimated by the investigator are collected and the acute Symptom Score (aSS) is evaluated (see Table 3).

Table 3: aSS (acute Symptom Score), evaluated by the investigator

Symptom Score (score 0 – 3)		
nasal symptoms	itchy nose	max (0–3*)
	sneezing	max (0–3*)
	runny nose	max (0–3*)
	congested nose	max (0–3*)
conjunctival symptoms	itching/reddened eyes	max (0–3*)
	watery eyes	max (0–3*)
Acute Symptom Score, ASS = sum of the numbers (evaluated by the investigator)		∑ Max score 18/6 (i.e. 4 nasal symptoms, max score 12 and 2 conjunctival symptoms, max score 6) = 3

*0 = no complaints; 1 = slight complaints (clearly present but hardly noticed); 2 = moderate Complaints (annoying but bearable); 3 = severe complaints (difficult to bear, disturbing daytime activities/sleep)

5.2 Rationale for the Study

This PMCF study is carried out according to the CE mark of a device and the device is used within its intended purpose and within its approved labelling. The study intends to confirm performance (effectiveness) and safety of the BICOM Optima/BICOM optima Mobil Device for bioresonance treatment in patients with allergic rhino-conjunctivitis in clinical routine use and in accordance with the current IFU. In this study it is evaluated whether patients in routine practice are achieving expected outcomes. The patient sample is representative of the average patient population. This is a heterogeneous population including children from the age of 4 years with few exclusion criteria. The exclusion criteria are in compliance with the IFU.

The study is conducted in accordance with the sponsor's Post Marketing Surveillance / Post market Clinical Follow up (PMS / PMCF) plan.

All study centers follow the clinical investigation plan and data are collected within routine clinical practice.

The device is a medical device (risk class IIa) for professional use. It is developed exclusively for use by trained, licensed therapists, state-approved naturopaths or trained medical professionals under their supervision.

The BICOM systems belong to the complementary medicine and aim to activate and restore the body's own self-healing powers using the BICOM bioresonance therapy method. The BICOM systems are recommended for the treatment of mild to moderate allergic and allergy-related diseases or complications, but focusing on allergic rhino-conjunctivitis.

BICOM Bioresonance therapy is a complementary medical practice in which it is proposed that low energy electromagnetic waves can be used to treat human illness.

Although several clinical studies could show a good performance of BRM devices with sustainable treatment success in allergic rhinitis and conjunctivitis (Ref. in CER: Schumacher, 1998, Huang 2005, Wang 2006, Yuan 2005, Yuan), a further study to confirm performance and safety is required.

This is required to confirm the results of the previous studies which have been mostly performed outside the EU and at a time, where clinical standards like the GCP and ISO 14155 norm did not exist. The ISO 14155 addresses good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the clinical performance or effectiveness and safety of medical devices. This PMCF study, being performed according to current GCP and ISO 14155 requirements, should confirm the results of the previous studies.

6 Investigational Device and Methods

6.0 Investigational Device Description

6.0.1 Description of the BICOM Devices

The BICOM optima device delivers bioactive fields on a low-energetic base. The electromagnetic oscillations are delivered from applicators, thereby no currents are transferred. The therapy frequency range spans 1 Hz to 250 kHz in the newer versions B32, B34, BM34 (see Figure 1 and Figure 2).

The BICOM optima is intended for short time usage without contact to damaged skin.

There are different types of applicators used, which are described in chapter 2.5. The applicators come into direct contact with the intact skin and are not allowed to be used with damaged skin. All materials of these applicators, the patient comes into contact with, are listed in Table 2-3. Duration of one therapy session lasts between 15 – 30 min.

The BICOM optima device comprises several stored therapy programs that have been developed and proven of value in the last 30 years of therapeutic application. The experienced user also can create and save own programs to achieve best possible therapy results in the intended medical field.

The patient is connected to the so-called device input and device output via applicators during the bioresonance method (BRM) treatment session. This is called “the biocybernetic control cycle” and enables the transfer of information via wave patterns of the patient, modification and feeding back of the modified signals to the patient via the output applicator. The input and output applicators are connected by cable with the bioresonance device. Through the input applicator, the electromagnetic signals are absorbed by the body and discharged through the output applicator. This description corresponds to the transfer of the body’s own wave patterns to the patient via channel 1.

Another treatment method is the transfer and modification of the information carrying wave pattern of any diagnostically and therapeutically relevant substance using an input beaker before retransfer via the output applicator to the patient. Simultaneous transfer of information of substances (e.g. medication) during the therapy via channel 1 is allowed by the 2nd channel. Moreover, the information of therapeutic substances and their specific electromagnetic wave patterns are stored and may be also used during bioresonance method. This feature (transfer of substances’ information via 2nd channel) is thought to enhance the success of the therapy like the well-known effect of homeopathic substances. In this way the stressed organ systems shall be stabilized and initial deteriorations (see side effects, chapter 2.9) shall be minimized.

The BICOM optima mobil is a device version designed for the mobile use and comprises all therapeutic functions of the pedestal unit. It is supplied with a trolley and a case and can be charged in the car (Figure 2).

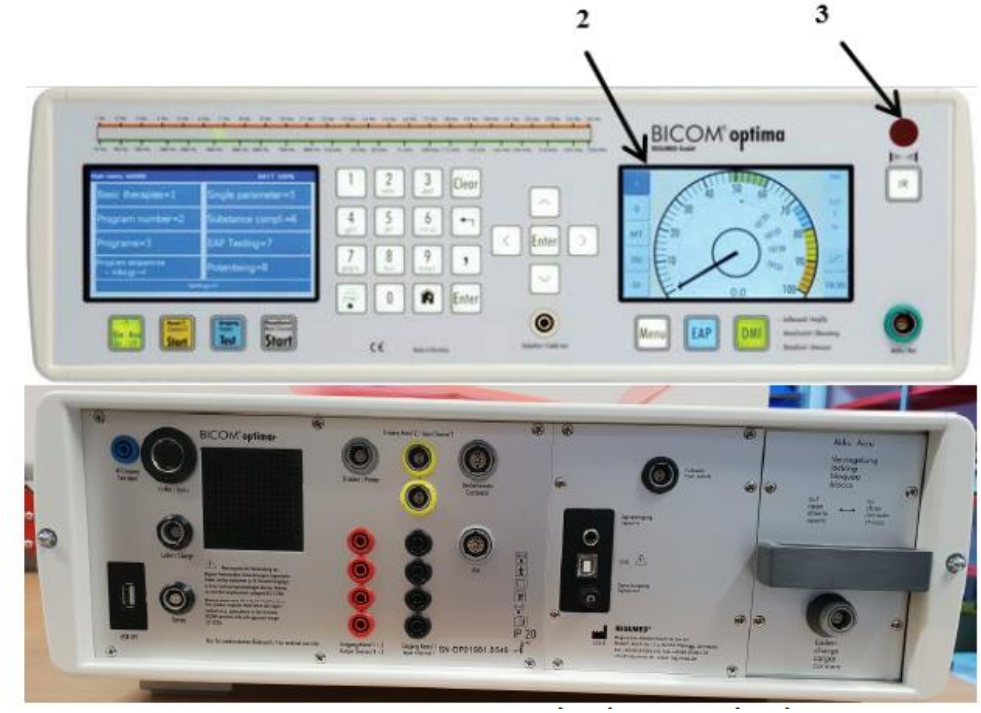


Figure 1: BICOM optima front (B34) and back (B32)

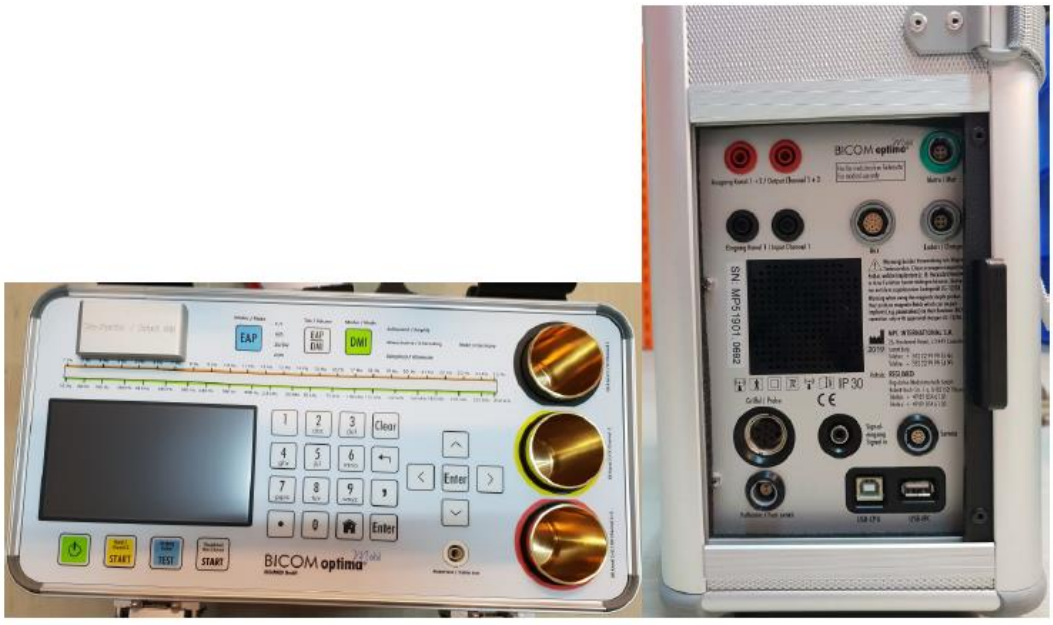


Figure 2: BICOM optima BM34 (mobile version), front and back

Figure 1:
2: Functions of the EAV-module are the measurement of the voltage (mV, millivolt) and current (µA, microampere) in the tissue of the mouth, optimization of the device settings as well as testing of allergens, medicaments and toxins. This method for the diagnosis of allergies is recommended to be used exclusively in addition to the common methods of school medicine.

3: The ISE receives electromagnetic spectra from ampules that contain a substance to be tested such as an allergen or medicament. Then the ISE transmits the electromagnetic oscillations either to the EAV-module or the therapy module.

On the left side of the front of the BICOM optima device there is the monitor and a scale that shows the used band pass determined by the chosen therapy program is located above. The screen displays the menu, the instrument setting and further information for the user. There are the optional components – the infrared transceiver (ISE), the electro-acupuncture (EAV) test module (Figure 1). EAV is a complementary method. The newer device versions offer two touchscreens and foil keypad, the mobile device versions BM34 comprises one touchscreen and the foil keypad. Just as in the older versions B24, B25, the display (new as touchscreen) can be found on the left side. Navigating through the display may be done by either using the touch screen function or by using the foil keypad. A second touch screen can be found on the right side of the BICOM optima. In this display the control functions for the EAP test part and in the full version the IR module can be found: On the back of the BICOM optima device there are all plug contacts except the ones for the cable test and the modulation mat, which are on the front of the device (Figure 1).

Device versions
The different device versions contain the same therapy module but differ in respect of the optional components (Table 4). The device versions comprise the same therapeutic functions and are identical regarding application.

Table 4: device versions

Model	EAP Module (optional)	ISE (optional)	Comments
B32	✓	X	
B34	✓	✓	
BM34	✓	X	Mobile version

NOTE: ✓ included; X not included;

Accessories

There are various types of applicators which are suitable for use with BICOM optima / BICOM optima mobil: plate applicators, cylindric applicators and spherical applicators that are sterilisable with ethanol, applicators with Teflon-coated grab handles for body hollows that are sterilisable with steam, flexible applicators with a conductive natural rubber layer and a clear protective film consisting of contaminant-free PVC and magnetic probes with up to 2900 Gs (magnet-depth-probes and magnet-joint-probes). The modulation mat is available in two different sizes (small and large).

The modulation mat represents the most often used applicator in BICOM bioresonance therapy. The modulation mats produce a weak magnetic field as a transport medium for therapy information whose magnetic field intensity is below that of the earth's magnetic field. The micro-impulses used have a very steep rising edge but are very low in intensity. The maximum measured value is about 10 µT. (The

Earth's field ranges between approximately 25 and 65 µT (0.25–0.65 Gauss)). All accessories are compatible with BICOM optima / BICOM optima mobil.

Table 5: Accessories (Ref. [2] in CER)

Accessory / component	Materials (of contact surfaces)	Tissue contact / Invasiveness	Cleaning	Disinfection /Sterilisation
Plate applicators	Brass (MS-CuZn37) PTFE/Teflon-coated grab handles Optional: cork overlay	Intact and damaged skin, but not open sores	BiClean applicator cleaner	wipe disinfection, e.g. with Bacillol AF (Bode Chemie GmbH); non-sterilizable
Flexible applicators	conductive graphite silicone-rubber layer RAU-SIK (with a clear protective film consisting of contaminant-free PVC without plasticizers (identical with modulation mat)	Intact and damaged skin, but not open sores	mild standard detergent	wipe disinfection, e.g. with Bacillol AF (Bode Chemie GmbH); non-sterilizable
Magnet depth-probes	grab handles and coating made of polyoxymethylene (POM, Polyacetal) stainless steel 1.4301 (X5CrNi18-10), AISI 304 (V2A);	Intact and damaged skin, but not open sores, skin/mucosa of the body hollows, teeth and tongue	mild standard detergent	wipe disinfection, e.g. with Bacillol AF (Bode Chemie GmbH); non-sterilizable
Magnet-joint-probes	stainless steel 1.4301 (X5CrNi18-10), AISI 304 (V2A) (contains nickel)	Intact and damaged skin, but not open sores	mild standard detergent	wipe disinfection, e.g. with Bacillol AF (Bode Chemie GmbH); non-sterilizable
Dental applicators	grab handles and coating: polytetrafluorethylene (PTFE/Teflon) applicator tip: stainless steel 316LVM (steel 1.4441) optional: conductive natural rubber layer (NR/SBR45)	Mucosa of the teeth and tongue	mild standard detergent, e.g. Microbac (Bode Chemie GmbH)	wipe disinfection, e.g. with Bacillol AF (Bode Chemie GmbH), heat sterilization (up to 134 °C)
Modulation mat	Contaminant-free PVC without plasticizers (identical with flexible applicators)	No direct skin contact required; though treatment with synthetic fiber clothes should be avoided;	mild standard detergent, e.g. Microbac (Bode Chemie GmbH)	wipe disinfection, e.g. with Bacillol AF (Bode Chemie GmbH); non-sterilizable
Screw brass applicator	Brass (MS-CuZn39Pb3 or MS-CuZn37)	Intact and damaged skin, but not open sores	mild standard detergent	wipe disinfection, e.g. with Bacillol AF (Bode Chemie GmbH); non-sterilizable
Special applicators				
Goldfinger applicator	grab handles and coating consists of polytetrafluorethylene (PTFE/Teflon) applicator head made of brass (MS-CuZn39Pb3) gold-plated	Intact and damaged skin, but not open sores, skin/mucosa of the body hollows, teeth and tongue	mild standard detergent, e.g. Microbac (Bode Chemie GmbH)	wipe disinfection, e.g. with Bacillol AF (Bode Chemie GmbH); Sterilisable (heat-resistant up to 134°C)
Headpones applicator	applicator head made of brass (MS-CuZn39Pb3) gold-plated	Skin of the ear canal	mild standard detergent, e.g. Microbac (Bode Chemie GmbH)	wipe disinfection, e.g. with Bacillol AF (Bode Chemie GmbH); non-sterilizable
Spherical applicator	brass (MS-CuZn37)	Intact and damaged skin of the hands, but not open sores	mild standard detergent, e.g. Microbac (Bode Chemie GmbH)	wipe disinfection, e.g. with Bacillol AF (Bode Chemie GmbH); non-sterilizable
Grab handle ("7-poliger Test- und Therapiegriffel")	Shank: brass (MS-CuZn37) Coating: polytetrafluorethylene (PTFE/Teflon)	Intact and damaged skin, but not open sores	mild standard detergent, e.g. Microbac (Bode Chemie GmbH)	wipe disinfection, e.g. with Bacillol AF (Bode Chemie GmbH); non-sterilizable

Technologies / Basic functionalities

There are different modes of therapy available:

- A: Delivery of filtered and enhanced/diminished electromagnetic oscillations of the body or a substance; used for the delivery of electromagnetic spectra of organo therapeutics, homeopathics, phytopharmaceuticals etc.; provocation of patients with blocked reactions.
- Ai: Filtered, phase-constant inversion of the electromagnetic spectra of the body or a substance; used for the treatment of allergies, intolerances and detoxification.
- A+Ai: Therapy modes A and Ai alternating (provocation and moderation alternating); used for patients with blocked reactions and toxic contamination.

- H: Separation of the physiologic from pathologic electromagnetic spectra and delivery of enhanced/diminished electromagnetic oscillations; used for patients with physical exhaustion.
- Di: Separation of the physiologic from pathologic electromagnetic spectra and delivery of the inverted pathologic electromagnetic spectra; used for patients with acute infections
- H+Di: Combination of mode H and mode Di; used for extremely stressed and/or energetic unbalanced patients

In BICOM bioresonance therapy no currents are transmitted to the patient. Current transfer is prevented by equipment of the device with an opto coupler. [Ref. 17, in CER] An amplifier is provided in the device to amplify the received input signal and to form the output signal from it. The output can also be attenuated or shifted in the opposite" direction" to the inputs (phase-constant inversion). Physical principles of the BICOM device are provided in the Technical Documentation. [Ref. 3, 4, in CER]

The BICOM optima (B32, B34 and BM34) provides a therapy range of 1 Hz – 250 kHz.

Material composition

The biological safety evaluation comes to the conclusion that the materials of the devices under evaluation and the accessories are biocompatible. [Ref. 2, in CER] As outlined in the biological safety evaluation the materials of the BICOM optima / BICOM optima mobil and its accessories are very-well established materials in the medical field. The materials come into contact with the human body of the patient and/or the therapist (intact or damaged skin – but no open sores – and/or mucosa of the body hollows, teeth and tongue) for a limited period of time.

The biocompatibility of the materials of the applicators was evaluated in the risk analysis. The materials, the therapist or the patient comes into contact with, are biocompatible. [Ref. 6, 15, in CER]

There are different types of applicators used and various types of applicators are suitable for use with BICOM optima / BICOM optima mobil: plate applicators, cylindric applicators and spherical applicators that are sterilisable with ethanol, applicators with Teflon-coated grab handles for body hollows that are sterilisable with steam, flexible applicators with a conductive natural rubber layer and a clear protective film consisting of contaminant-free PVC and magnetic probes with up to 2900 Gs (magnet-depth-probes and magnet-joint-probes). The modulation mat is available in two different sizes (small and large).

The modulation mat represents the most often used applicator in BICOM bioresonance therapy. The modulation mats produce a weak magnetic field as a transport medium for therapy information whose magnetic field intensity is below that of the earth's magnetic field. The micro-impulses used have a very steep rising edge but are very low in intensity. The maximum measured value is about 10 µT. (The Earth's field ranges between approximately 25 and 65 µT (0.25–0.65 Gauss)).

All accessories are compatible with BICOM optima / BICOM optima mobil.

The applicators come into direct contact with the intact skin and are not allowed to be used with damaged skin. All materials of these applicators, the patient comes into contact with, are listed in Table 5. Duration of one therapy session lasts between 30 – 45 min.

6.0.2 Description of the medical method

Bioresonance therapy is a complementary medical practice in which it is proposed that low energy electromagnetic waves can be used to treat human illness. The system is available in three variants. BICOM optima B32, B34 are stationary devices, whereas BICOM optima BM34 mobile is a portable device used for complementary medical therapy.

The BICOM systems belong to the complementary medicine and aim to activate and restore the body's own self-healing powers using the bioresonance therapy method. The BICOM systems are recommended for the treatment of mild to moderate allergic and allergy-related diseases or complications but focussing on allergic rhino-conjunctivitis.

Bioresonance is based on knowledge gained from research in the field of quantum physics. One of the elementary findings of this branch of science is that all matter has two constituents: the particle itself and radiation. A specific electromagnetic field can be assigned to every particle of matter. This principle may also be applied to every cell or every organ of the human body. The bioresonance method uses electro-magnetic cell communication in order to support the body's regulation and self-healing processes.

For diagnosis or therapy, the patient is connected with the BICOM system by means of input applicators. Through these applicators the patient's own information transmitted through specific wave patterns pass to the device, where they are processed by the BICOM system depending on the condition being treated and the therapy program being applied and then fed back to the patient via the output applicator.

Current, well-known technical medical diagnostic systems, e.g. EEG, ECG, EMG, MRT, MEG use external, technically generated electromagnetic fields for diagnostic and therapeutic purposes. The bioresonance method is based on the scientifically proven fact, known for some fifty years, that living organisms generate measurable bioelectromagnetic fields. The BICOM system picks up the information from substances or patients in these electromagnetic fields by means of applicators (surface applicators = flat aerials) and transmits them back to patients through output applicators. The wave pattern which carries the information may be transferred by the device in attenuated, unchanged, amplified or inverted form, or conditioned with a band pass filter. The collection and onward transmission of the biophysical information is carried out using magnetic applicators. Different setting options allow the therapist to modify the information. The patient is connected to the input and output of the device with flexible applicators and forms a therapeutic (bio cybernetic) control circuit with the device during therapy.

This information is fed back within the spectral range from 1 Hz to 250 kHz - split into two spectral ranges 1 Hz to 25 Hz and 10 Hz to 250 kHz.

The BICOM systems are operated and controlled by means of keyboard, keypad keys and touchscreen.

Therapy channel I: By separating the body's own information into physiological and pathological components using a special filter (BICOM Separator), different therapy options can be identified. In addition, pathological information can be changed by inversion, amplification, attenuation, and selection of specific band pass modes of the wave which is transmitting the information.

Therapy channel II: A separate, 2nd channel allows the transmission of accompanying or supporting information and the wave patterns from homoeopathic and/or naturopathic remedies. The setting is always therapy type A, with the signal remaining unchanged. Both therapy time and amplification (amplitude) can be modified, however.

Digitised substance-specific information and their wave patterns may also be transferred to the patient via channel 2.

All therapy signals lie below the thermal noise level.

Accompanying or supportive transfer of micro-magnetic field impulses, wave patterns (Dynamic Multi Impulse = DMI) mimicking Schumann waves and sferics, in increasing, reducing or alternating

frequency sequences from 1 Hz to 1000 Hz. The field strength in each case (app. 7 µT) lies ten times below that of the earth's magnetic field (app. 70 µT).

The patient's initial energetic state is determined using Dr Voll's electro acupuncture testing (EAP).

General technical function

The function of the BICOM optima device is broadly similar to that of an audio amplifier which has a throat microphone at one end and a loudspeaker at the other. The voice (sound information) is mechanically picked up at the throat, where the vocal cords are located. The oscillations are then processed to generate an electric signal. This signal is amplified/filtered by means of an audio amplifier and reproduced as a sound wave through a loudspeaker.

With the BICOM systems, the patient is connected to the device by means of input applicators. The patient is galvanically isolated from the device by means of an optocoupler. The signals are transmitted via the input applicator to the device, processed according to the type of therapy being administered (see below) and then fed back to the patient via the output applicator.

The signals are transmitted via the input applicator to the device, processed according to the type of therapy being administered and then fed back to the patient via the output applicator.

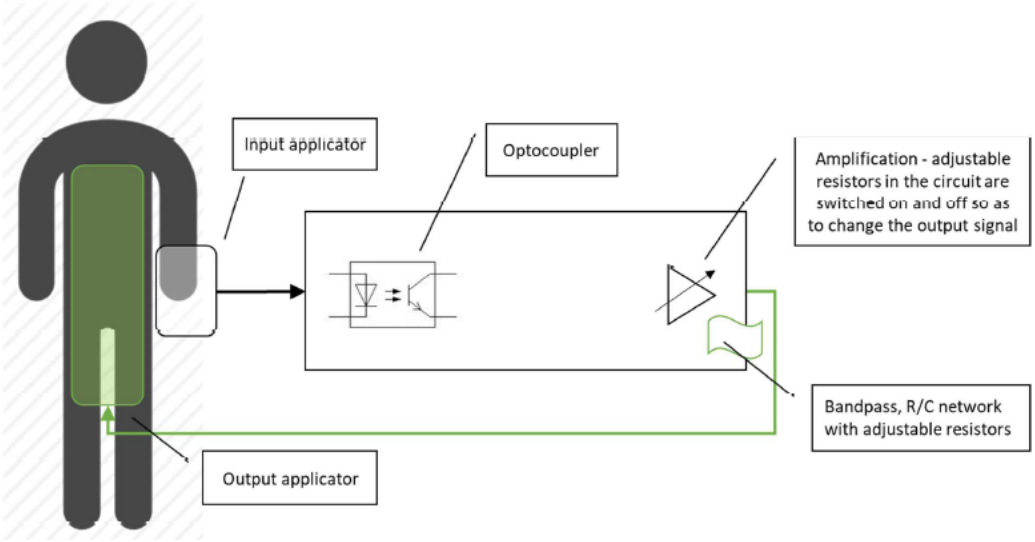


Figure 3: BICOM optima - Signal transmission

6.0.3 Intended Use and Indication of Investigational Device

The BICOM systems belong to the complementary medicine and aim to activate and restore the body's own self-healing powers using the bioresonance therapy method. The BICOM systems are recommended for the treatment of mild to moderate allergic and allergy-related diseases or complications, but focusing on allergic rhino-conjunctivitis.

Bioresonance therapy is a complementary medical practice in which it is proposed that low energy electromagnetic waves can be used to treat human illness. The BICOM system is recommended for use with adults and children aged 4 years and older.

The device is a medical device (risk class IIa) for professional use. It was developed exclusively for use by trained, licensed doctors, state-approved naturopaths or trained medical professionals under their supervision.

Medical indication

The BICOM systems belong to the complementary medicine and aim to activate and restore the body's own self-healing powers using the bioresonance therapy method. The BICOM systems are recommended for the treatment of mild to moderate allergic and allergy-related diseases or complications, but focusing on allergic rhino-conjunctivitis.

Contraindication/Warnings/Side effects

Contraindications, warnings, precautions and identified potential risks of the BICOM optima device are outlined in the current instruction for use [Ref. 5, in CER] and the risk analysis [Ref. 6, in CER] in detail.

Contraindications:

1. Exceptions are medical emergencies or suspected medical emergencies. The BICOM system shall not be used as a primary treatment in these situations.

2. Treatment of patients with transplanted organs can be contraindicated, also treatment of immunosuppressed patients after organ transplantations. The application may only be carried out after careful consideration of the individual patient by a physician. Those patients shall not be treated with the dynamic multi-impulse therapy.

3. Treatment of patients with active implants can be contraindicated. The application may only be carried out after careful consideration of the individual patient by a physician.

4. Treatment of patients with active bleeding, and haemophiliacs or treatment of bleeding-prone patients can be contraindicated. The application may only be carried out after careful consideration of the individual patient by a physician.

5. Treatment of hyperergic or anaphylactic patients can be contraindicated. The application may only be carried out after careful consideration of the individual patient by a physician.

6. Treatment of patients suffering from epilepsy or cramps can be contraindicated. The application may only be carried out after careful consideration of the individual patient by a physician.

7. Treatment of severe cardiac disorders can be contraindicated. The application may only be carried out after careful consideration of the individual patient by a physician.

8. Treatment during the first three month of pregnancy can be contraindicated. The application may only be carried out after careful consideration of the individual patient by a physician.

9. Patients should not consume alcohol on the day of treatment.

10. During treatment: if unpleasant feelings such as dizziness, nausea or head pressure occur during therapy or at the end of therapy, the therapy should be stopped briefly until patient feels better.

11. The applicators of the device shall not be used directly on injured skin.

Side effects:

The IFU explains the following:

The known side effects can be summarized as following:

- Mild amplification of the existing symptoms (initial exacerbation, short term)
- Headache
- Vertigo
- Fatigue
- Mild nausea

- Low-grade fever
- Increased excretion of secrets, urine, and faeces
- Diarrhea
- Increased redness of the skin
- Allergic reaction to nickel because of materials of chip

6.0.4 Previous intended uses or indications for use, if relevant

NA

6.0.5 Changes to the Investigational Device during the Study or any Changes from the Investigator's Brochure

NA

6.0.6 Changes in the instruction for use

No changes have been made to the instructions for use during the course of this clinical investigation.

6.1 Clinical Investigational Plan (CIP)

6.1.1 Study Objectives and Endpoints

Objective of the PMCF-study was to assess performance and safety of the BICOM optima/BICOM optima Mobil for bioresonance therapy in patients with mild to moderate allergic rhino-conjunctivitis.

6.1.2 Primary Study Objectives and Endpoints

Primary Objective	Endpoint for Primary Objective
Performance (Effectiveness) - Effect of BICOM-treatment on symptom severity (reduction of the severity of symptoms)	• Mean weekly Symptom Score (wSS): Captured from the second allergy treatment session until one week after the last allergy treatment in the study and compared to baseline. A maximum of 8 allergy treatments with the BICOM bioresonance therapy will be considered.
Safety:	• Adverse Device Effects (ADE), device and / or procedure related • Serious adverse device effects (SADE), device and / or procedure related

6.1.3 Secondary Study Objectives and Endpoints

The secondary study objectives are the evaluation of the need for medication, quality of life and acute symptoms at the days of treatment before and during the bioresonance allergy treatment:

Secondary Objectives	Endpoints for Secondary Objectives
Quality of Life (QoL), before and during the bioresonance allergy treatment	• Mean Quality of Life Score (QoLS) as measured by a questionnaire
Mean need for medication, before and during the bioresonance allergy treatment	• 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)	• 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.

Explorative endpoints are:

Symptoms, Quality of Life Score and need for medications in the preparation phase (treatments without allergy specific programs) compared to baseline.

6.1.4 Study Design

This is a prospective, multi-center, single-arm, open-label, observational PMCF study.

The patients will be treated according to the clinical routine and in accordance with the current IFU.

This PMCF study is carried out according to the CE mark of a device and the device is used within its intended purpose and within its approved labelling. The study intends to confirm performance (effectiveness) and safety of the BICOM Optima/BICOM Optima Mobil Device for bioresonance treatment in patients with allergic rhino-conjunctivitis in clinical routine use and in accordance with the current IFU. In this study it will be evaluated whether patients in routine practice are achieving expected outcomes. The patient sample is representative of the average patient population. This is a heterogeneous population including children from the age of 4 years with few exclusion criteria. The exclusion criteria are in compliance with the IFU.

The study is conducted in accordance with the sponsor's Post Marketing Surveillance / Post market Clinical Follow up (PMS PMCF) plan.

All study centers follow the clinical investigation plan and data is collected within routine clinical practice.

6.1.5 Ethical Considerations

The trial is carried out in accordance with the national requirements (e.g. the German Medical Devices Act), with the international standard ISO 14155 Clinical investigation of medical devices for human subjects - Good clinical practice, and with the ethical principles of the declaration of Helsinki, revised version. In addition, the applicable data protection regulations - in particular the EU General Data Protection Regulation (EU GDPR) - in its respective applicable version have been considered.

In compliance with the professional code of practice (§15 “Berufsordnung der Ärzte”), ethics committee advice has been obtained before starting with study.

This was a post-market study according to §23b German Medical Devices Act (MPG) with the aim of gathering clinical data related to the device in question. The clinical investigation did not involve procedures additional to those performed under the normal conditions (i.e. no additional invasive or burdensome procedures).

The following category criteria were fulfilled:

- Clinical study with a medical device that bears the CE mark and is applied within its intended use.
- Study according to §23b German Medical Devices Act (MPG); observational study.

6.1.6 Data Quality Assurance

The study has been conducted in accordance with the current approved protocol, ISO 14155:2020, ICH GCP, as far as applicable and relevant regulations and standard operating procedures.

The PI was responsible for proper training of all involved study personnel.

6.1.7 Electronic Case Report Forms (eCRF)

The study data will be entered and documented in electronic case report forms (eCRF). The eCRFs are created to collect all necessary demographic and clinical data and to evaluate the collected parameters as described in this clinical investigation plan. The eCRF is completed by the investigator or by members

of the study team and then electronically signed by the principal investigator or an authorized investigator. Detailed instructions and an explanation of how to complete the eCRF will be provided.

Users only get access to the eCRF after they have received training and instruction. The access authorization to the eCRF system is restricted to read and write rights depending on the user in order to guarantee the highest possible data integrity.

Each participant in the study will be assigned a unique code by the EDC system, which protects their identity by using the patient code as a pseudonym in the eCRF. Only the investigator and the study team know the identities behind the patient code. The main examiner keeps a list of the patient codes assigned to each patient. The list is a confidential document that must be stored in the study documentation and can be viewed by the monitor.

The Principal Investigator must ensure the accuracy and completeness of the recorded data and then provide his/her signature on the appropriate CRFs. Changes to data previously submitted to the sponsor will require a new signature by the Investigator to acknowledge/approve the changes.

The site staff will be responsible for resolving all queries in the database.

6.1.8 Study source documents

Study source documents consist of the medical records of the respective study center. The source data is used to verify the data entered in the eCRF to ensure quality of data. Source data is not entered directly into the eCRF.

6.1.9 Archiving

The study center retains all documents - in particular the documents relevant for the identification and traceability of the participating patients - and all original data for at least 10 years after the end of the study. The Investigator is responsible to ensure that the study documents are archived in a secure location for the duration required by local regulations.

Regumed - Regulative Medizintechnik GmbH will retain all study records and eCRF data for 10 years.

6.1.10 Data management

An electronic data capture system (EDC) will be used for the conduct of this study. The data management system used will be provided by a certified contract provider. After the data has been entered into the eCRF, it will be saved and transmitted to a secure server via a secure connection.

The EDC system and database have been validated and are compliant with legal regulations applicable for electronic data storage and electronic signatures. Database backups will be performed regularly. Data are transmitted to a server with secured connection. The server is protected with mechanisms to prevent unauthorized access.

The data management procedures are described in the study-specific data management plan.

Data entered by the site will be reviewed by the CRA (Clinical Research Associate/Monitor) for missing entries, consistency and plausibility. During on-site monitoring visits, the CRA also compares the eCRF data with the source data. Data management also reviews the data as defined in the DMP. In case of questionable, inconsistent or missing data, queries will be raised by the CRA or data management, to be resolved by the site personnel in a timely manner.

After the study has ended, when data passed a set of validation procedures (e.g. forms closed, no outstanding queries open etc.) the database is closed, so that no further entries are possible. After the

database lock, the data is transmitted from eCRF provider to CERES for analysis and reports. The data is evaluated using the statistical analysis plan (SAP).

6.1.11 Monitoring

The study will be monitored in compliance with the Declaration of Helsinki, ISO 14155:2020, the CIP, the signed agreement and all applicable national regulations. Trained and qualified monitors, who will document each individual monitoring visit, will conduct all monitoring activities.

The Investigator will permit a representative of Regumed - Regulative Medizintechnik GmbH, or delegated representatives, to inspect all electronic Case Report Forms (eCRF) and the corresponding patient's medical records at regular intervals throughout the clinical investigation.

In general, during onsite monitoring visits the monitor will ensure that the study is being conducted according to the CIP, ISO 14155:2020, ICH-GCP (International Conference on Harmonization – Good Clinical Practice), as far as applicable, and other applicable regulations. He/she will also make sure the informed consent procedure has been appropriately carried out and will ensure that all SADEs/ incidents have been reported within applicable timeframes. He/she will also ensure that critical endpoint data is properly recorded. The monitor will also ensure that the site personnel maintain the regulatory documents of the study adequately.

All data transmitted by the study staff in the eCRF will be verified by the monitor as part of the remote monitoring in mutual coordination with the study. Incomplete or unclear data sets are resolved with the study centers using queries so that high data quality can be achieved.

For quality purposes and for the purposes of source data verification (SDV), independent risk-based on-site monitoring will be carried out by the monitor. For this purpose, corresponding monitor visits will be planned in the study centers, during which the study centers will be visited in accordance with the study specific monitoring plan.

Detailed monitoring procedures including the frequency of onsite visits and extent of source data verification are described in a separate monitoring plan.

6.1.12 Audits and Inspections

The study can be subject to an audit by the sponsor or by a third party commissioned on behalf of the sponsor. Furthermore, inspections can be carried out by the authorities or audits can be carried out by a notified body. In such cases, it must be ensured that the auditors / inspectors have unhindered access to all relevant study data at the study centers. All involved persons must keep the data of the study participants confidential. The study staff must be available for questions during audit / inspection.

6.1.13 Confidentiality and Data Protection

Data protection of patient's personal health data was ensured and data were treated confidentially.

All data protection requirements must be respected. The Sponsor treated all data in accordance with the national legal requirements and in accordance with the European GDPR (General Data Protection Regulation).

The principal investigators provided the sponsor and their representatives and regulatory authorities access to all source data and electronic data, as far as applicable.

6.1.14 Study Subject Population

Inclusion Criteria:

Based on routine clinical practice, a patient can be enrolled in the study according to the IFU and if the following criteria are met:

a. symptomatic seasonal or perennial allergic rhino-conjunctivitis without severe asthma
b. Patient with mild to moderate allergic symptoms
c. Therapist expects that the treatment will usually compromise two preparation sessions and at least three allergic specific sessions within 15 weeks.
d. Patient is 4 years and older
e. Signed written informed consent to participate in this clinical trial and willingness and ability to participate in this study

Exclusion Criteria:

Patients may not participate in the study if they meet at least one of the following conditions:

a) Psychiatric conditions and/or inability to provide informed consent
b) Off-label use (application is not within the IFU)
c) Exclusion of subjects based on the contraindications in the IFU

Sample Size

Approx. 132 patients are to be included in this observational study. Both men and women of 4 years and older with mild to moderate rhino-conjunctivitis can be included in the study. That includes all patients with allergy-related symptoms and/or complications meeting the inclusion and exclusion criteria of the study.

6.1.15 Treatment and Treatment Allocation Schedule

The patient receives the standard treatment as part of the clinical routine and in accordance with the instructions for use. The follow-up visits are carried out at the study center according to clinical routine. The time windows of the individual visits correspond to the usual clinical routine.

With the BICOM systems, the patient is connected to the device by means of input applicators. The patient is galvanically isolated from the device by means of an optocoupler. The signals are transmitted via the input applicator to the device, processed according to the type of therapy being administered (see below) and then fed back to the patient via the output applicator.

Signals are fed from and to the patient by analog transmission.

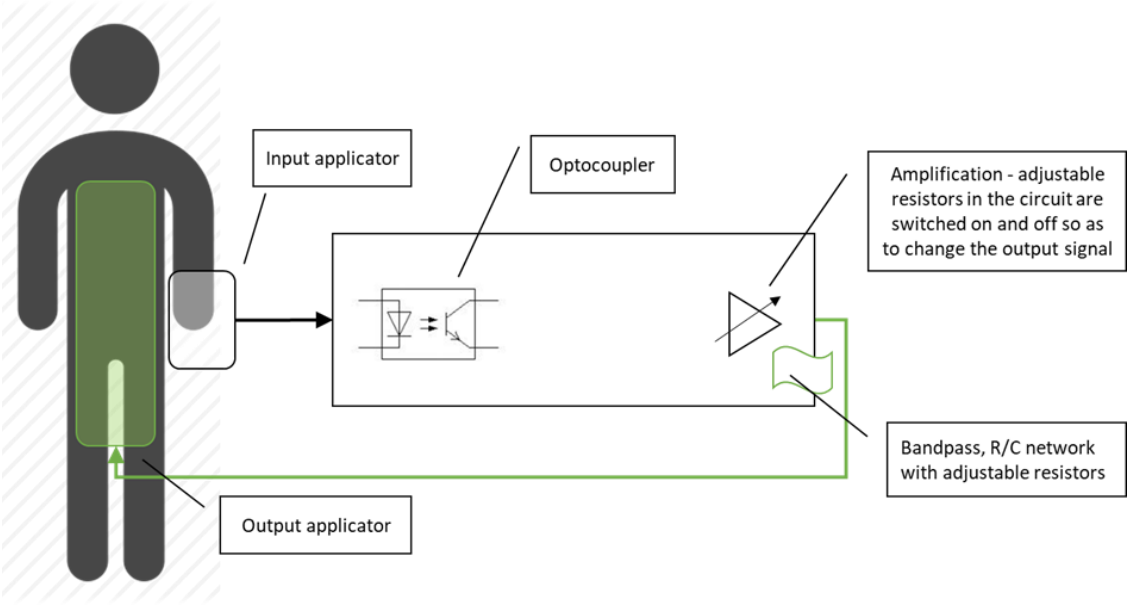


Figure 4: General technical functioning

The patients must be informed before they can be treated with the BICOM bioresonance therapy that they should not consume alcohol on the day of treatment.

During the treatment the investigator pays attention if unpleasant feelings such as dizziness, nausea or head pressure occur during therapy or at the end of therapy. In the occurrence of this case the therapy should be stopped briefly until patient feels better.

It is also important to ensure that the applicators of the device shall not be used directly on injured skin.

Measurement:

The patients will usually undergo up to 2 preparation sessions, at least 3 and a maximum of 8 BICOM bioresonance allergy treatment sessions with treatment free intervals of one to two weeks. The duration of the allergy treatment period (treatment phase) will take from at least 3 up to a maximum of 13 weeks, adapted to the patient's response to the therapy. If a patient requires more than 8 allergy treatment sessions, the data collection for treatment is terminated with the 8th treatment session or after 15 weeks of treatment whatever comes first. All patients will get afterwards a one week follow up. Follow up data can be collected before the start of a BICOM treatment after end of treatment in the investigation.

Each BICOM bioresonance treatment session is divided into different parts that contain a selection of programs. The preparation treatment sessions usually are used to improve the responsiveness of the organism and to remove therapy blockages (See study schedule treatment session 1 and 2). They include programs for basic therapy, blockage-releasing programs and programs for cleansing and balancing of the body from an energetic viewpoint. From the third treatment session, blockage-releasing programs and programs for cleansing and balancing of the body and the specific allergy treatment programs and supporting symptom-related programs will be applied (See study schedule treatment session 3 up to 10).

Before every treatment session and one week follow up after the last allergy treatment relevant for study, the symptom score, the medication score, the Quality of Life questionnaire data and the actual symptoms estimated by the investigator are collected.

The collected data represents always the status of the patient in the week before measurement with exception of the actual symptoms. This also applies, if more than a week has passed between two treatment sessions.

It is possible to include patients in the study who have already received bioresonance therapy in the past. These patients will not receive any pre-treatment.

ADE/SADE will be collected from the first preparation treatment until the last treatment within the study.

Table 6: Study schedule:

	Visit 1 (optional)	Visit 2 (optional)	Visit 3 to Visit max 10, if applicable	EOS for each patient
	Preparation Treatment Session 1	Preparation Treatment Session 2	Allergy Treatment Session 3 up to Session 10	one week Follow up after the last allergy treatment
Informed consent [a)]	X			
Anamnese [a)]	X			
Demographic data [a)]	X			
Symptom Score [a), b)]	X	X	X	X
Medication Score [a), b)]	X	X	X	X
Actual Symptom Score by investigator [a)]	X	X	X	X
Quality of Life Questionnaire [a), c)]	X	X	X	X
Energetic testing [d)]	X	X	X	
Basic treatment [e)]	X	X		
Blockage -releasing treatment [f)]	X	X	X	
Elimination treatment [g)]	X	X	X	
Allergy treatment [h)]			X	
ADE/SADE Recording [i)]	X	X	X	

** One week follow-up take place one week after the last allergy treatment session*
Note: *Before each Treatment session, including the two "preparation treatment" which include basic treatment, blockage -releasing treatment and elimination treatment, the patient's symptom score, the actual symptom score by the investigator, the medication score, and the Quality of Life questionnaire are recorded.*

a) *Patients who do not receive preparation-treatment will be enrolled in the study before start of the first allergy treatment.*
b) *adapted according to Pfaar Allergy. 2014 Jul;69(7):854-67; The strongest symptoms and their duration in days are recorded and the recording of medication, including the duration of medication in days*
c) *Quality of life questions are evaluated for the influence of the rhino-conjunctivitis on 7 topics with 5-point rating scales and 5 topics for children*
d) *Energetic testing: According to the clinical routine.*
e) *Selection of a basic therapy program or a sequence from this category by conductance value. The basic therapy sequencies should not be used as individual programs, but the selected sequence should be run through completely.*
f) *Select one, max. 3 blockage-releasing therapy programs or a program sequence of this category after bioenergetic testing.*
g) *Select one, max. 3 elimination programs or a program sequence of this category after bioenergetic testing*
h) *Select programs from Category 4: Allergy therapy and supportive symptom-related programs or a program sequence from this category. If possible, the program sequencies should not be split up, but should be used completely. Please select max. 1 program sequence per session and, if necessary, an additional program or max. 4 individual programs.*
i) *Adverse device effects (ADE) and serious adverse device effects (SADE) were recorded from the first treatment session. Be aware of that also, the first worsening of the treated symptoms and the duration of the first aggravation should be reported as (S)ADE.*

6.1.16 Concomitant Medications/Treatments

The medication of the patients' allergy medication is to be documented in the case report form.

6.1.17 Duration of Follow-up

The patients will usually undergo up to 2 preparation sessions, at least 3 and a maximum of 8 BICOM bioresonance allergy treatment sessions with treatment free intervals of one to two weeks. The duration of the allergy treatment period (treatment phase) will take from at least 3 up to a maximum of 13 weeks, adapted to the patient's response to the therapy. If a patient requires more than 8 allergy treatment sessions, the data collection for treatment is terminated with the 8th treatment session or after 15 weeks of treatment whatever comes first. All patients will get afterwards a one week follow up. Follow up data can be collected before the start of a BICOM treatment after end of treatment in the investigation.

6.1.18 Statistical Analysis

All documented data is subjected to a descriptive statistical analysis. Categorical data are presented with absolute and relative frequencies, the primary target parameter and the frequency of adverse events are also presented with 95% confidence intervals according to Clopper-Pearson. Continuous and quasi-continuous data are described using the following parameters: number, mean, standard deviation, 95% confidence interval of the mean, minimum, quartile (25% quartile, median, 75% quartile) and maximum.

Should p-values be calculated not mentioned in primary and secondary analysis (e.g., in subgroup comparisons), these are reported explicitly without reference to hypotheses. Unless otherwise specified, p-values are calculated two-sided.

If the change variables are markedly non-normally distributed and the subsamples are smaller than 30 then Kruskal-Wallis test and Wilcoxon rank-sum test will be used respectively.

A detailed statistical analysis plan (SAP) has been prepared.

6.1.19 Study Hypothesis

Treatment leads to a mean reduction of wSS of at least 1 point (minimally important difference (MID), Devillier 2014) compared to baseline.

6.1.20 Sample Size Calculation

At least a reduction in the mean symptom score during treatment of 1 point (Devillier 2014) has been expected. Given this effect size, and a measurement with a standard deviation of 3.3, 88 subjects are necessary to show this effect with a two-sided one sample t-test at $\alpha = 0.05$ and a power = 80%. Due to the unfavorable circumstances up to 12 drop outs are anticipated.

100 patients, 12 years and older had to be included for formal testing of device efficiency.

Additionally, 32 children between 4 up to 11 years had to be included to demonstrate performance and safety for this age group.

In total 132 subjects had to be included into the investigation.

6.1.21 Statistical Analysis Methods

Data sets and populations to be analysed

All patients treated with BICOM optima/BICOM optima Mobil allergy treatment and supportive symptom-related programs at least at one visit and a follow-up visit with measurement for the primary endpoint (full analysis set) will be analyzed for effectiveness on primary and secondary endpoints.

All patients treated with BICOM optima/BICOM optima Mobil at least in one visit (safety analysis set) will be analyzed for safety. These patients are also the basis for the description of the sample (demography, diagnosis).

Possible groups for subgroup analysis are kind of allergy (pollen, mite dust and animal hair), gender and age group (children, adolescents, adults).

Children 4 up to 11 years will be analyzed separately.

6.1.22 Primary Analysis

Primary analysis for efficiency is a one sample two-sided t-test or Wilcoxon signed-rank test for comparison of the mean weekly symptom score at treatment with the baseline symptom score. Primary analysis for safety is the frequency of adverse events by patients presented with 95% confidence intervals according to Clopper-Pearson. If applicable SAE, SADE be presented in separate tables.

6.1.23 Secondary Analysis

Secondary analyses for efficiency are one sample two-sided t-tests or Wilcoxon signed-rank test for comparison of the mean quality of life score and mean medication score at treatment with the baseline quality of life score respectively medication score.

All parameters collected that are not covered by the primary and secondary efficiency analysis or the safety analysis are evaluated descriptively according the scale level of the parameters.

6.1.24 Explorative Analysis

Multiple regression analysis will be conducted for identifying potential factors influencing performance of BICOM treatment. In this analysis children are included. Preplanned independent parameters are age group, gender, number of allergic treatments sessions, kind of allergy and duration of rhino-conjunctivitis.

The preparation treatment sessions are for general preparation with an unspecific effect on symptoms. Symptom scores, quality of life score and medication following this session will be evaluated exploratory. Data captured before second preparation treatment and before the first allergy treatment represent this phase. Mean scores be compared with the respective baseline values.

6.1.25 Sensitivity Analysis

The symptoms of allergic rhino-conjunctivitis depend on the actual exposure to allergens. In the case of pollen allergies, the exposure changes seasonally, and in the case of multiple allergies, there may be temporal overlaps. In order to assess this influence on the results of the study, sensitivity analyses are carried out to determine whether and how regional and temporal exposure to pollen affects the

symptoms of known pollen allergies. Additionally, sensitivity analysis is carried out into account anti-allergic medication.

6.1.26 Safety Analysis

Adverse events are presented descriptively with relative and absolute frequencies and the 95% confidence interval according to Clopper-Pearson for incidences.

6.1.27 Changes to the Clinical Investigational Plan

Changes to the CIP are summarized in Table 7

Table 7: Changes to the CIP Release Date	**Version**	**Reason for Change**
19.11.2020	1.0	Initial Version
14.01.2021	2.0	Adaption of the statistical analysis according to EC request and editorial revision of inconsistencies

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 not included 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).

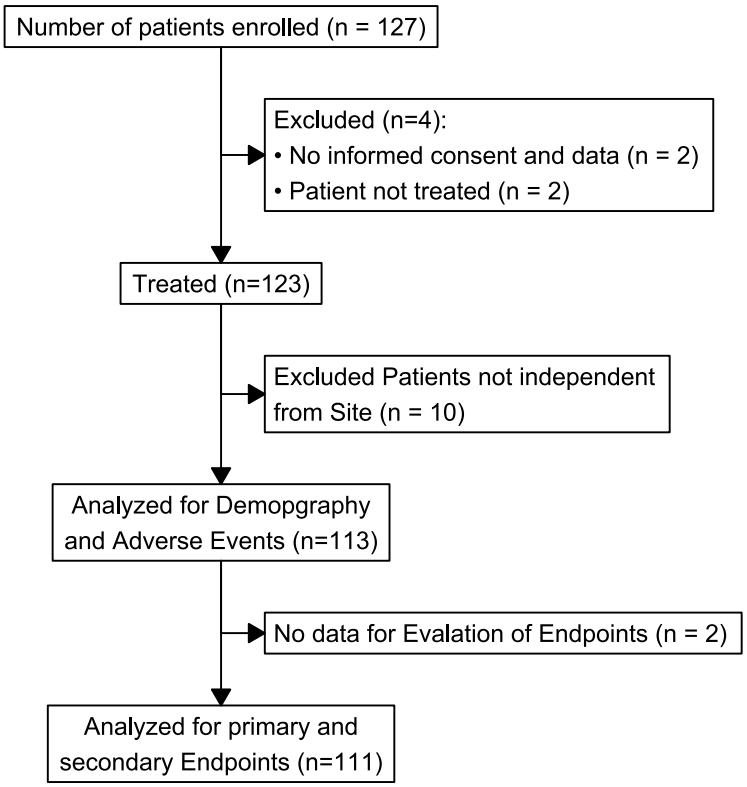


Figure 5: Disposition

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/m^2]					
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 (± 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.

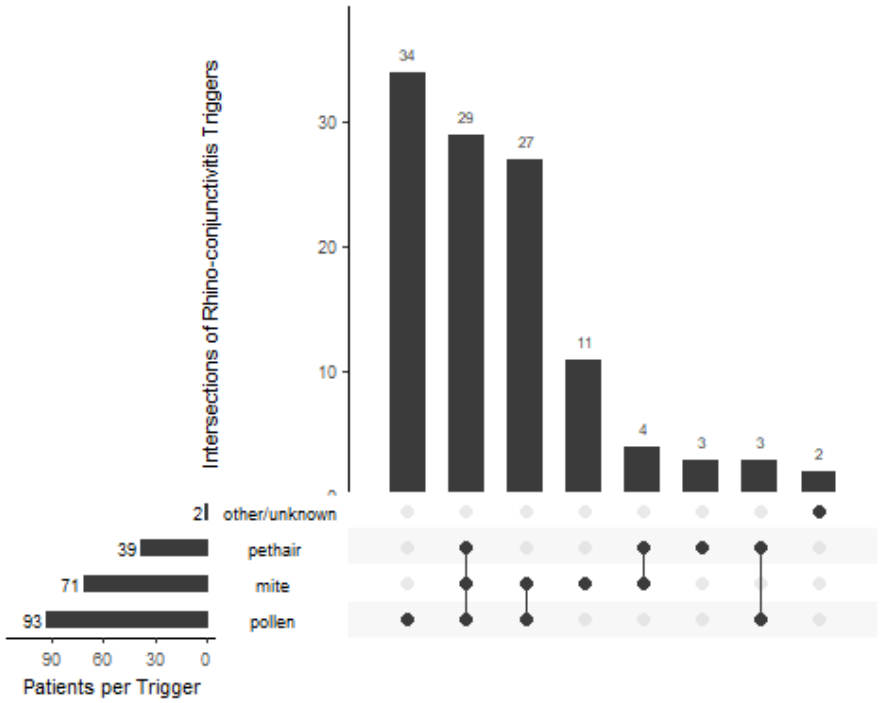


Figure 6: Known Triggers for Rhino-conjunctivitis

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 compromise 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; ***[1]**113 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 = ½ 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	• Mean Quality of Life Score (QoLS) as measured by a questionnaire
Mean need for medication (before and during the bioresonance allergy treatment)	• 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)	• 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

*[1]113 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 N = 111*[1]	Children aged 4-11 N = 28	Youths aged 12-17 N = 14	Patients (≥ 12) N = 83	Adults (≥ 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

***[1]**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)
***[1]**113 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 Baselien - 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 weeklys 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 ≥ .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 repectively 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.

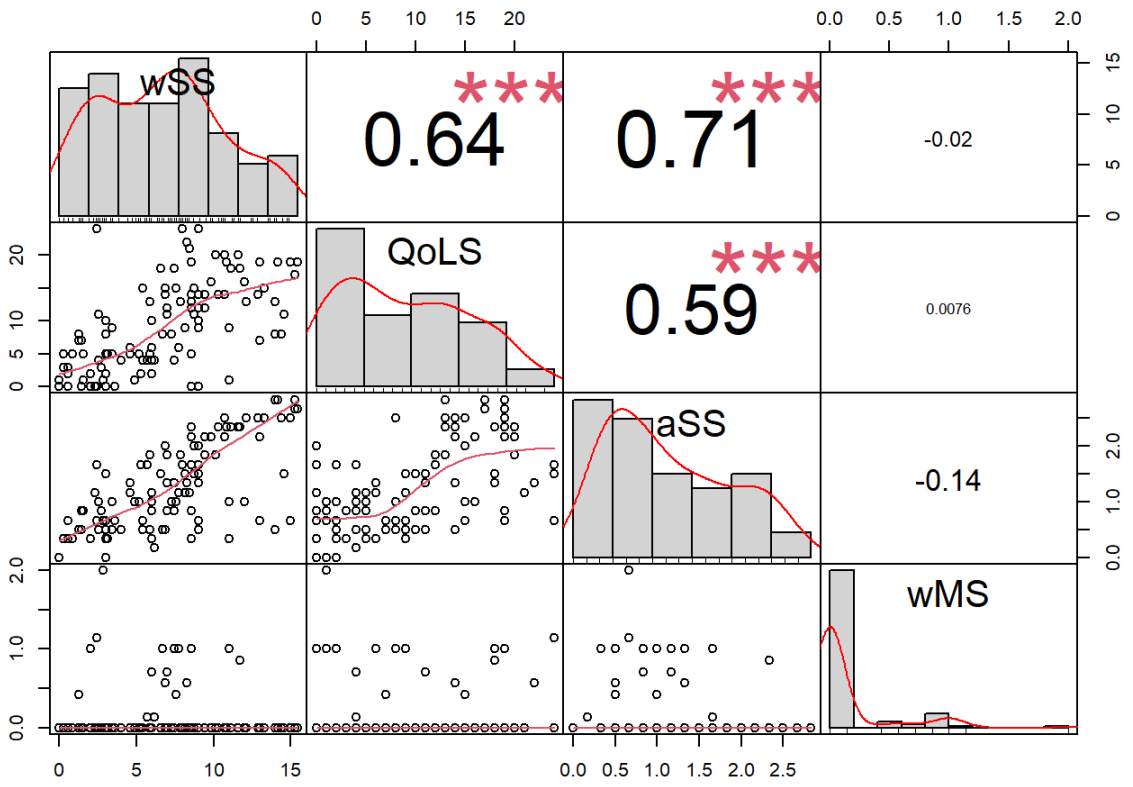


Figure 7: Correlations, Histograms and Scatterplots for Outcome Measures at Baseline

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.

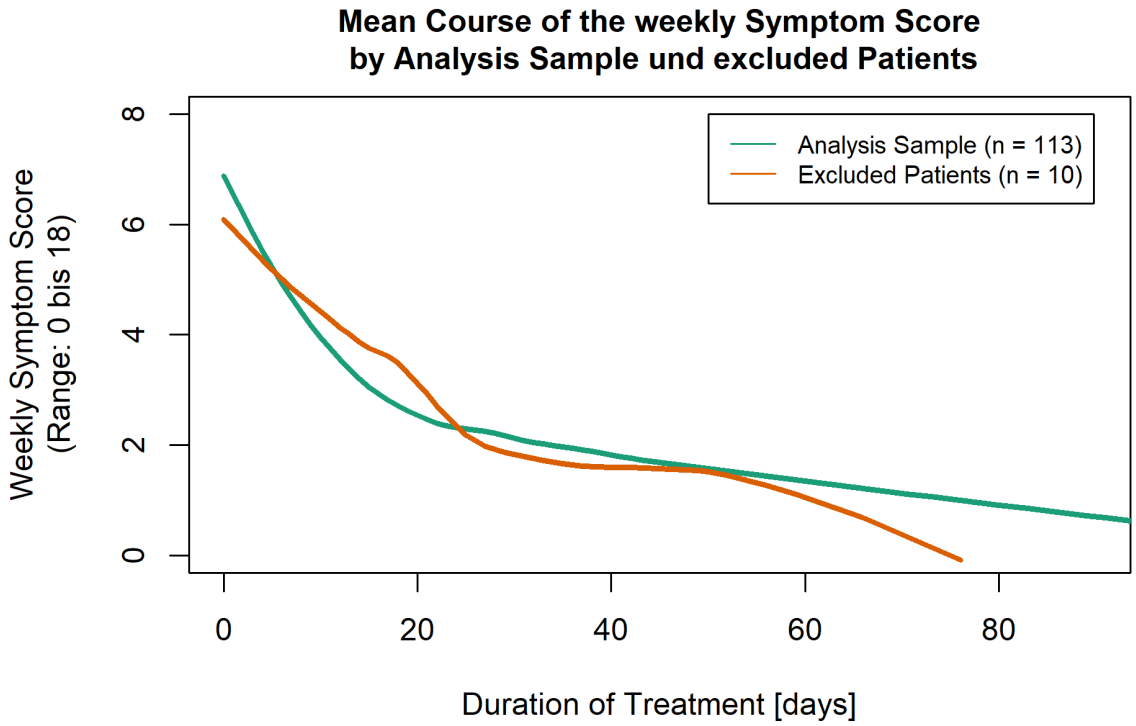


Figure: 7 - 1: Mean Course of the weekly Symptom Score by Analysis Sample und excluded Patients

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

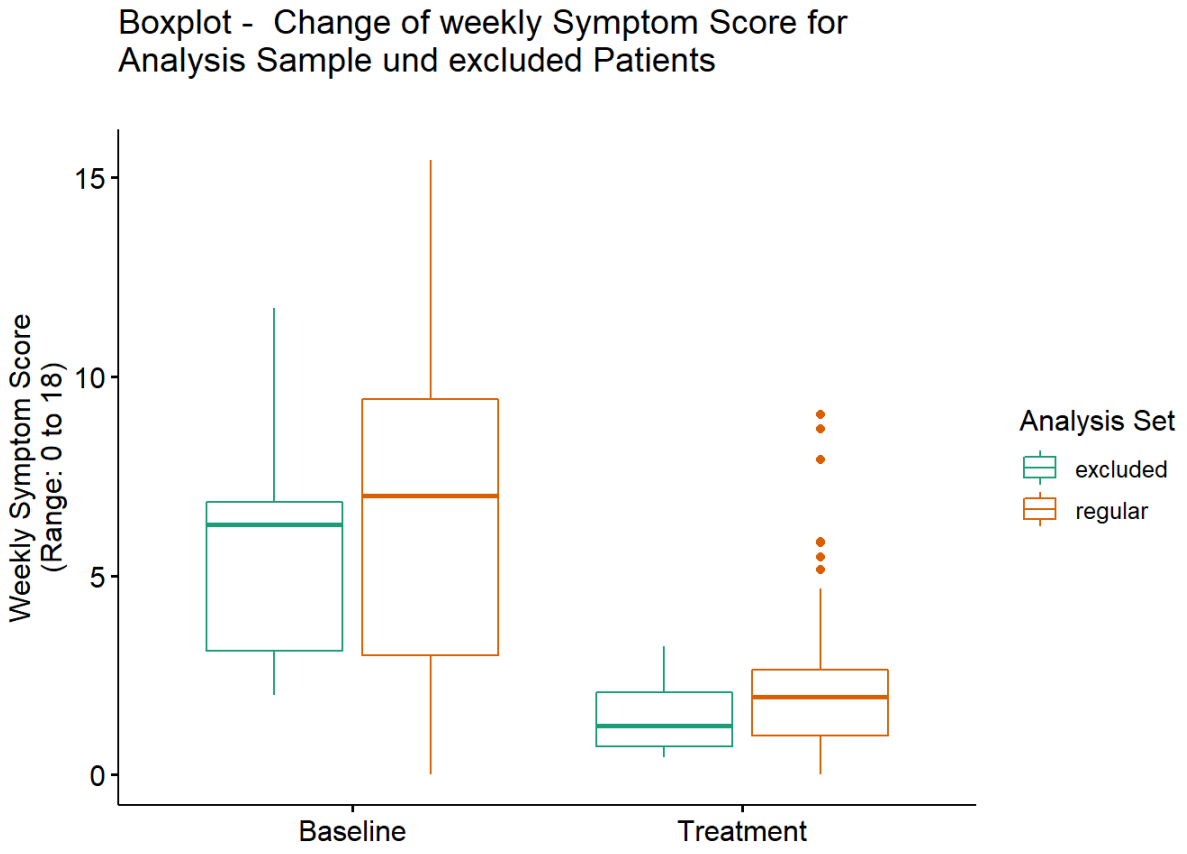


Figure: 7 - 2: Weekly Symptom Score for the Analysis Sample an excluded Patients - Boxplot

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 try 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 investigates 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.

9 Abbreviated Terms and Definitions

A list of abbreviated terms is provided below:

Table 29: Abbreviations

Abbreviation	Term
AE	Adverse event
AIT	Allergy Immunotherapy
AR	Allergic Rhinitis
ARC	Allergic Rhino-conjunctivits
aSS	Acute Symptom Score
BRT	Bioresonance Treatment
CIP	Clinical Investigational Protocol
CRF	Case report form
CSR	Clinical Study Report
dSS	daily Symptom Score
DCSMS	Daily Combined Symptom and Medication Score
EMA	European Medicines Agency
FDA	Food and Drug Administration
IEC	Independent ethics committee
IFU	Instructions For Use
MID	minimally important difference
(S)ADE	(Serious) Adverse Device Effect
SAE	Serious adverse event
QoL	Quality of Life
QoLS	Quality of Life Score
QoLQ	Quality of Life Questionnaire
wMS	weekly Medication Score
wSS	weekly Symptom Score

10 Ethics and regulatory Approval

10.0 Independent Ethics Committee Approval

This is a post-market study according to §23b German Medical Devices Act (MPG), exemption, with the aim of gathering clinical data related to the BICOM Devices family of Regulative Medizintechnik GmbH. The investigational device bearded a CE mark and was used according to the IFU. The clinical investigation did not involve procedures additional to those performed under the normal conditions (i.e. no additional invasive or burdensome procedures).

This is a study outside of the German Medical Devices Act (exemption) and in accordance with the professional code of practice (§15 "Berufsordnung der Ärzte"). In compliance with this, ethics committee advice has been obtained before starting with study.

Advices from the following involved ethics committees have been received:

- Ethikkommission Ärztekammer Nordrhein, dated 20.01.2021 (Ref. 2020393)
- Ethik-Kommission der Ärztekammer Nordrhein, e-mail dated 12.02.2021. The EC acknowledges the vote/advice of EC Ärztekammer Nordrhein.

10.1 Patient Information and Consent

All patients included so far into the study provided written informed consent to participate in the study prior to being screened.

The patient information informed about the study with regard to data protection, the use of their medical treatment data in the study and the right to withdraw from the study at any time without specification of reasons in writing. The investigator explained these to each patient. The patient signed the consent form to indicate that the information had been explained and understood. The patient was given a copy of the informed consent form for their information. The original copy of the informed consent was kept in a confidential file in the Investigators centre records.

10.2 Regulatory Approval

As the study was an exemption of the Medical Devices Act (§23 b), no approval from a regulatory authority was required.

11 Investigators and administrative Structure of clinical Investigation

11.0 Study Organization

The BICOM study is sponsored by Regulative Medizintechnik GmbH and administered by CERES GmbH Evaluation & Research.

11.1 List of Investigators

The following investigators are taking part in the study:

Investigator	**Address**	**Federal State**
Dr. med. Jürgen Hennecke **Coordinating PI**	Trierer Straße 133 52078 Aachen	North Rhine-Westphalia
Marie Christin Etti	Stadttor 1 40219 Düsseldorf	North Rhine-Westphalia
Dr.med. Susanne von Ohlen	Hospitalstraße 7 37073 Göttingen	Lower Saxony
Dr.med. Karin Bösler	Mittelstraße 25 30900 Wedemark	Lower Saxony
Dr. med. Tobias Schipper	Am Rechter 6 26655 Westerstede	Lower Saxony
Dr. Julia Berg	Mühlstraße 3 92318 Neumarkt i.d.OPf	Bavaria
Dr. med. Uta Schmieden-Lindner	Bahnhofstraße 16 92648 Vohenstrauß	Bavaria
Dr. med. Richard Baustädter	Dorfstraße 34 94089 Neureichenau	Bavaria

11.2 Third Party Organizations

Name and address of the involved study Clinical Research Organization is listed below:

CRO
CERES GmbH evaluation & research
Brombacher Str. 85
79539 Lörrach
Germany

11.3 Sponsor(s) or Representative(s)

Regumed,

Regulative Medizintechnik GmbH

Robert-Koch-Str. 1 a

82152 Planegg

Germany

Tel.: +49 (0) 174 9080940

Email: r.wollenzin@regumed.de

12 References

References Cited in the Clinical Study Report:

ARIA 2016; Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, Brignardello-Petersen R, Canonica GW, Casale T, Chavannes NH, Correia de Sousa J, Cruz AA, Cuello-Garcia CA, Demoly P, Dykewicz M, Etxeandia-Ikobaltzeta I, Florez ID, Fokkens W, Fonseca J, Hellings PW, Klimek L, Kowalski S, Kuna P, Laisaar KT, Larenas-Linnemann DE, Lødrup Carlsen KC, Manning PJ, Meltzer E, Mullol J, Muraro A, O'Hehir R, Ohta K, Panzner P, Papadopoulos N, Park HS, Passalacqua G, Pawankar R, Price D, Riva JJ, Roldán Y, Ryan D, Sadeghirad B, Samolinski B, Schmid-Grendelmeier P, Sheikh A, Togias A, Valero A, Valiulis A, Valovirta E, Ventresca M, Wallace D, Waserman S, Wickman M, Wiercioch W, Yepes-Nuñez JJ, Zhang L, Zhang Y, Zidarn M, Zuberbier T, Schünemann HJ. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol. 2017 Oct;140(4):950-958. doi: 10.1016/j.jaci.2017.03.050.

ARIA 2008; Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, Zuberbier T, Baena-Cagnani CE, Canonica GW, van Weel C, Agache I, Aït-Khaled N, Bachert C, Blaiss MS, Bonini S, Boulet LP, Bousquet PJ, Camargos P, Carlsen KH, Chen Y, Custovic A, Dahl R, Demoly P, Douagui H, Durham SR, van Wijk RG, Kalayci O, Kaliner MA, Kim YY, Kowalski ML, Kuna P, Le LT, Lemiere C, Li J, Lockey RF, Mavale-Manuel S, Meltzer EO, Mohammad Y, Mullol J, Naclerio R, O'Hehir RE, Ohta K, Ouedraogo S, Palkonen S, Papadopoulos N, Passalacqua G, Pawankar R, Popov TA, Rabe KF, Rosado-Pinto J, Scadding GK, Simons FE, Toskala E, Valovirta E, van Cauwenberge P, Wang DY, Wickman M, Yawn BP, Yorgancioglu A, Yusuf OM, Zar H, Annesi-Maesano I, Bateman ED, Ben Kheder A, Boakye DA, Bouchard J, Burney P, Busse WW, Chan-Yeung M, Chavannes NH, Chuchalin A, Dolen WK, Emuzyte R, Grouse L, Humbert M, Jackson C, Johnston SL, Keith PK, Kemp JP, Klossek JM, Larenas-Linnemann D, Lipworth B, Malo JL, Marshall GD, Naspitz C, Nekam K, Niggemann B, Nizankowska-Mogilnicka E, Okamoto Y, Orru MP, Potter P, Price D, Stoloff SW, Vandenplas O, Viegi G, Williams D; World Health Organization; GA(2)LEN; AllerGen. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA (2)LEN and AllerGen). Allergy. 2008 Apr;63 Suppl 86:8-160. doi: 10.1111/j.1398-9995.2007.01620.x.

Blaiss 2018; Blaiss MS, Hammerby E, Robinson S, Kennedy-Martin T, Buchs S. The burden of allergic rhinitis and allergic rhinoconjunctivitis on adolescents: A literature review. Ann Allergy Asthma Immunol. 2018 Jul;121(1):43-52.e3. doi: 10.1016/j.anai.2018.03.028.

Calderon 2014; Calderon MA, Bernstein DI, Blaiss M, Andersen JS, Nolte H. A comparative analysis of symptom and medication scoring methods used in clinical trials of sublingual immunotherapy for seasonal allergic rhinitis. Clin Exp Allergy. 2014 Oct;44(10):1228-39. doi: 10.1111/cea.12331. PMID: 24773171.

Corren 2017; Jonathan Corren, Allergic Rhinitis and Conjunctivitis, in Book: Middleton's Allergy Essentials 2017. DOI: 10.1016/B978-0-323-37579-5.00008-8.

Cuesta-Herranz 2019; Cuesta-Herranz J, Laguna JJ, Mielgo R, Pérez-Camo I, Callejo AM, Begoña L, Gomez MC, Madariaga B, Martinez A. Quality of life improvement with allergen immunotherapy treatment in patients with rhinoconjunctivitis in real life

conditions. Results of an observational prospective study (ÍCARA). Eur Ann Allergy Clin Immunol. 2019 Sep 16;51(5). doi: 10.23822/EurAnnACI.1764-1489.104.

Devillier 2014; Devillier P, Chassany O, Vicaut E, de Beaumont O, Robin B, Dreyfus JF, Bousquet PJ. The minimally important difference in the Rhinoconjunctivitis Total Symptom Score in grass-pollen-induced allergic rhinoconjunctivitis. Allergy. 2014 Dec;69(12):1689-95. doi: 10.1111/all.12518.

Nelson 2017; Nelson HS, Calderon MA, Bernstein DI, Casale TB, Durham SR, Andersen JS, Esch R, Cox LS, Nolte H. Allergen Immunotherapy Clinical Trial Outcomes and Design: Working Toward Harmonization of Methods and Principles. Curr Allergy Asthma Rep. 2017 Mar;17(3):18. doi: 10.1007/s11882-017-0687-0. PMID: 28293909.

Pfarr 2014; Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW, Durham SR, Jacobsen L, Malling HJ, Mösges R, Papadopoulos NG, Rak S, Rodriguez del Rio P, Valovirta E, Wahn U, Calderon MA; European Academy of Allergy and Clinical Immunology. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. Allergy. 2014 Jul;69(7):854-67. doi: 10.1111/all.12383.

Referenced CER:

Clinical evaluation report (CER), 20200804-799-BCM-Clinical Evaluation-Rev B.00, dated 19.11.2020

References mentioned in the CER:

Hossenbaccus 2020; Hossenbaccus, L.; Linton, S.; Garvey, S.; Ellis, A. K., Towards definitive management of allergic rhinitis: best use of new and established therapies. Allergy Asthma Clin Immunol 2020, 16, 39.

Huang 2005; Huang, S. (2005). Klinische Beobachtung der Behandlung vom allergischen Schnupfen und Bronchialasthma der Kinder mit dem Bioresonanztherapiegerät. Zhe Jiang Medizin, 27(6).

Langen 2013; Langen, U., Schmitz, R., & Steppuhn, H. (2013). [Prevalence of allergic diseases in Germany: results of the German Health Interview and Examination Survey for Adults (DEGS1)]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz, 56(5-6), 698-706. doi:10.1007/s00103-012-1652-7.

Rajakulendran 2018; Rajakulendran, M., Tham, E. H., Soh, J. Y., & Van Bever, H. P. (2018). Novel strategies in immunotherapy for allergic diseases. Asia Pac Allergy, 8(2), e14. doi:10.5415/apallergy.2018.8.e14.

Randall 2018; Randall, K. L., & Hawkins, C. A. (2018). Antihistamines and allergy. Aust Prescr, 41(2), 41-45. doi:10.18773/austprescr.2018.013.

Robert Koch Institut, 2018; Robert Koch Institut. (2018). KiGGS Welle 2 – Gesundheitliche Lage von Kindern und Jugendlichen. Journal of Health Monitoring, 3. doi:10.17886/RKI-GBE-2018-075.

Scheiblhofer, 2018; Scheiblhofer, S., Thalhamer, J., & Weiss, R. (2018). DNA and mRNA vaccination against allergies. Pediatr Allergy Immunol, 29(7), 679-688. doi:10.1111/pai.12964

Schuhmacher 1990; Schumacher, P. (1990). Biophysikalische Allergietherapie. Originalia

Schuhmacher 1998; Schumacher, P. (1998). Biophysikalische Therapie des Heuschnupfens Biophysikalische Therapie der Allergien.

Seidman 2015; Seidman, M. D., Gurgel, R. K., Lin, S. Y., Schwartz, S. R., Baroody, F. M., Bonner, J. R., Dawson, D. E., Dykewicz, M. S., Hackell, J. M., Han, J. K., Ishman, S. L., Krouse, H. J., Malekzadeh, S., Mims, J. W., Omole, F. S., Reddy, W. D., Wallace, D. V., Walsh, S. A., Warren, B. E., Wilson, M. N., Nnacheta, L. C., & Guideline Otolaryngology Development Group, A.-H. (2015). Clinical practice guideline: Allergic rhinitis. Otolaryngol Head Neck Surg, 152(1 Suppl), S1-43. doi:10.1177/0194599814561600.

US Department of Health and Human Services, 2007; US Department of Health and Human Services. (2007). Guidelines for the Diagnosis and Management of Asthma.

Wang 2006; Wang, J. (2006). Klinische Studie der Therapie von allergischem Asthma und allergischer Rhinitis mit dem BICOM2000. Institut für Regulative Medizin Gräfelfing, RTI Heft, 30.

Yang 2004; Yang, J., & Zhang, L. (2004). Clinical efficacy observation of treating 300 cases of childhood asthma using the BICOM2000 bioresonance therapy device.

Yuan; Yuan, Z. The clinical results of BICOM2000. Retrieved from Department of Pediatrics of Xi'an Central Hospital.

Yuan 2005; Yuan, Z. (2005). Klinische Ergebnisse mit dem BICOM2000 Bioresonanzgerät. Retrieved from Department of Pediatrics of Xi'an Central Hospital.

References of documents mentioned in the CER:

[2]: 20200804-799-BCM-Expertassessment-Rev A.00

[3]: 20200804-799-BCM-Product Description-Rev A.00

[4]: Physical Principles of the BICOM device, version 01, 02/2019

[5]: 20200814-799-BCM-Handbuch-Rev B.00

[6]: 20200420-799-BCM-Risik Management File - Rev A.00

[15]: 20200804-799-BCM-PMCF Plan-Rev B.00

[17]: 20200416-799-BCM-Intended Use-Rev C.00

13 Annexes to the Report

13.1

Statistical Analysis Report: SAR_ARC003en_BICOM_optima_final _V1.0

13.2

Clinical Investigation Plan: CIP_ARC003en_BICOM optimaPMCF Study_V.2.0

13.3

Instructions for Use (IFU), current version

13.4

List of principal investigators

Not applicable. Provided in section 11.1.

13.6

List of names and addresses of any external organizations

Not applicable. Provided in section 11.2.

13.7

List of ECs:

Not applicable. Provided in section 10.0.

Annex A: Index of Figures

Annex B: List of Tables