CLINICAL INVESTIGATION REPORT

CLINICAL INVESTIGATION TITLE:

A clinical investigation of **K**inetic **O**scillation **S**timulation by the PBASE system in the treatment of **I**diopathic **R**hinitis (KOSIR)

SHORT TITLE: PBASE system Idiopathic Rhinitis Clinical Investigation

Study Code:	PR003
Clinical Investigational Medical Device:	PBASE system
Device classification:	IIa
Clinical Investigation design:	Interventional, multi-centre, double-blind, placebo-controlled investigation in patients diagnosed with idiopathic rhinitis.
Study period:	First Subject Randomized: 2013-04-18 Last Subject Completed: 2014-08-27
Date of Report:	FINAL; 2015-01-05
Ref no.:	1002144A
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This clinical investigation was conducted in accordance with Note for Guidance on Good Clinical Practice (GCP): CPMP/ICH/135/95, January 1997 (where applicable to medical devices) and the principles of the European Standard EN ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice.

1 SIGNATURES

I have read this report and confirm that to the best of my knowledge

it accurately describes the conduct and results of the Clinical Investigation.

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2 SYNOPSIS

Name of Sponsor/Company: Chordate Medical AB	
Clinical Investigational Medical Device: PBASE system	**Device classification:** IIa
Clinical Investigation Title: A clinical investigation of **K**inetic **O**scillation **S**timulation by the PBASE system in the treatment of **I**diopathic **R**hinitis (KOSIR) **Short Title:** PBASE system Idiopathic Rhinitis Clinical Investigation	
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Studied period: Date of first randomization:2013-04-18 Date of last subject completed: 2014-08-27	

Name of Sponsor/Company: Chordate Medical AB	
Clinical Investigational Medical Device: PBASE system	**Device classification:** IIa

Objectives

Primary objective

To evaluate the performance of the PBASE system, in terms of the efficacy of treatment with the device upon Total Vasomotor Rhinitis Symptom Score (TVRSS).

Secondary objectives

a) To evaluate the efficacy on individual nasal symptom scores and Peak Nasal Inspiratory Flow (PNIF)

b) To evaluate the efficacy on health related quality of life

c) To evaluate the safety of the PBASE system

Study design

This was an interventional, multi-centre, double-blind, placebo-controlled investigation in patients diagnosed with idiopathic rhinitis.

Methodology

The clinical investigation consisted of a screening visit (Visit 1), a seven day run-in period followed by two treatment visits (Visits 2 and 3) and two follow-up visits (Visit 4 and 5). In addition, a follow-up telephone call was performed in between Visits 4 and 5.

Patients diagnosed with idiopathic rhinitis were informed about the clinical investigation verbally and in written before any study-specific procedures were performed. More detailed information about the informed consent process is provided in section 5.3.

Consenting subjects were screened for eligibility at Visit 1 (Screening Visit). Eligible subjects entered a prospective baseline period of seven days, starting from the day following Visit 1. The subject was asked to complete an electronic diary on a daily basis, between the Screening Visit and the 8 week follow-up visit (Visit 4) and thereafter during the week prior to the remaining follow-up (3 month Telephone follow-up, and Visit 5). The average intensity of nasal symptoms during the previous 24 hours, use of rescue medication and change in concomitant medications during the previous 24 hours were recorded in the diary.

The first treatment visit (Visit 2; Day 1; Week 0) took place within 7-9 days from Visit 1. After eligibility had been confirmed based on diary data and a pregnancy test for women of childbearing potential, eligible subjects were randomized to active treatment or to control. Randomization was performed by allocating subjects to a randomization letter (A, B, C, D, E or F) linked to a specific connector on the CT100 module of the investigational device corresponding to either control or active treatment.

The second treatment visit (Visit 3) took place 4 weeks after Visit 2 (Day 28 ± 3 days). All subjects were given active treatment at this visit. For blinding purposes, randomization was performed and subjects were allocated to one of three connectors on the investigational device delivering active treatment (totally six connectors whereof three delivering control).

Treated subjects were followed up by telephone and visits; 8 week follow-up (Visit 4; Day 56 ± 7 days), 3 month telephone follow-up (Day 84 ± 7 days), and 6 month follow-up (Visit 5; Day 168 ± 7 days).

Name of Sponsor/Company:
Chordate Medical AB

Clinical Investigational Medical Device:	**Device classification:**
PBASE system	IIa

Duration of each subject's involvement in the clinical investigation

The duration of each subject's involvement was 6 months and 7-9 days, including run-in and follow-up.

Number of subjects (planned and analysed):

	Active	**Placebo**	**Total**
Number of subjects planned	79	79	158

The sample size was recalculated following the planned interim analysis (see section 9.8.1.3):

	Active	**Low amplitude control**	**Placebo**	**Total**
Revised number of subjects planned	80	48	79	207

	Active	**Low amplitude control**	**Placebo**	**Total**
Actual number of subjects randomized	81	48[1]	79	208

Subjects Randomized	208
Subjects receiving treatment 1	207
Subjects receiving treatment 2	199
Subjects in the Full Analysis Set (FAS)	207
Subjects in the Per Protocol Analysis Set (PPAS)	170
Subjects in the Safety Analysis Set	207

Clarification note: The control procedure used before the first interim analysis is in the report called Low amplitude control and was used for 47 subjects whereas the control procedure used following the first interim analysis is called Placebo and was used for 79 subjects. In the efficacy/performance analyses the main comparisons have been made between active treatment and Placebo only (81+79=160 subjects in the FAS). In tables with descriptive statistics presented also for the Low amplitude control, the Active group has been divided into subjects treated before and after the first interim analysis ("Old" and "New" Active, respectively).

[1] One subject was randomized by mistake and was therefore not treated.

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Clinical Investigational Medical Device: PBASE system	**Device classification:** IIa

Diagnosis and main criteria for inclusion

Male and female patients, 18-65 years of age, with persistent (>12 weeks) symptoms of idiopathic rhinitis dominated by nasal congestion were considered for participation in this clinical investigation. Detailed inclusion and exclusion criteria are listed in section 9.4.

Clinical Investigational Medical Device(s)

PBASE system (PBASE Device 1.1 [Ref no 1001337] and Catheter A100 [Ref no 1001245]), BALL fixation device (Ref no 1001152).

The PBASE system is used to stimulate human tissue inside the nasal cavities by means of mechanical pressure and oscillations at low frequencies. The device is an active therapeutic device intended to administer energy. The system is intended to be used by healthcare professionals in a clinical environment. It is CE marked for the treatment of non-allergic rhinitis.

Reference Medical Device:

The control/Placebo module CT100 (Ref no 1001152) connected to the PBASE system was developed to be able to conduct double blind placebo controlled clinical investigations.

The Low amplitude control treatment differed from the active treatment by giving much lower amplitude of the kinetic oscillations compared to the active treatment. After the first interim analysis, the control treatment was modified to just insert the balloon into the nostrils without neither inflating the catheter nor stimulating the mucosa by oscillations (Placebo).

Criteria for evaluation:

Primary performance/effect endpoint

Change in weekly mean TVRSS from baseline to Week 4 (Visit 3). The difference between subjects receiving active treatment at the first treatment visit and subjects receiving Placebo has been analysed.

Secondary performance/effect endpoints

- Change in weekly mean TVRSS from baseline to Week 8 (Visit 4), Week 12 and week 24 (Visit 5). The difference between subjects receiving two active treatments and subjects receiving one Placebo and one active treatment has been analysed.
- Change in weekly mean of each individual symptom score (nasal congestion, rhinorrhea, postnasal drip and sneezing).
  - The difference in change from baseline to Week 4 between subjects receiving active treatment at the first treatment visit and subjects receiving Placebo has been analysed.
  - The difference in change from baseline to Weeks 8, 12 and 24 between subjects receiving two active treatments and subjects receiving one Placebo and one active treatment has been analysed.
- Change in PNIF from baseline up to Week 4 (presented descriptively by treatment; Active/ Placebo) and to Weeks 8 and 24 (presented descriptively by treatment group; Active + Active/Placebo +

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Clinical Investigational Medical Device: PBASE system	**Device classification:** IIa

Active)

- Change in rhinosinusitis-specific quality of life, according to the Sino-Nasal Outcome Test 22 (SNOT-22) questionnaire, up to Week 4 (presented descriptively by treatment; Active/ Placebo) and to Weeks 8 and 24 (presented descriptively by treatment group; Active + Active/Placebo + Active)
- Change in functional disability and health-related quality of life, according to the EuroQol 5D-3L (EQ-5D-3L) questionnaire, to Week 4 (presented descriptively by treatment; Active/ Placebo) and to Weeks 8 and 24 (presented descriptively by treatment group; Active + Active/Placebo + Active)
- Use of rescue medication (number of days with rescue medication presented descriptively)

Safety endpoints

Evaluation of the frequency, severity, device-relationship and outcome of Adverse Events (AEs).

Statistical methods:

The change from baseline in weekly mean TVRSS has been analysed using an analysis of covariance (ANCOVA) model. The model included treatment and baseline mean TVRSS as covariate. Least square means (adjusted for the baseline value) for each treatment group and the difference in the least square means have been presented along with the corresponding 95% confidence interval and p-value. The primary analyses has also been performed by sex (males, females), type of diagnosis (non-allergic rhinitis, rhinitis medicamentosa, combination) and age (18 - <35, 35 - <50, 50-65).

Change from baseline in weekly median nasal congestion symptom score, rhinorrhea symptom score, postnasal drip symptom score and sneezing symptom score has been analysed using a proportional odds model. The model included treatment and weekly median baseline value of the symptom score as covariates and tested the difference between treatments (Active versus Placebo for Week 4 and two active treatments versus one active treatment for Weeks 8, 12 and 24). The Score test for proportional odds assumption in SAS has been used to test the assumption that all logit surfaces were parallel. A non-significant test was taken as evidence that the logit surfaces were parallel and that the odds ratios could be interpreted as constant across all possible cut points of the outcome. None of the tests were significant and thus extended Mantel-Haenszel analyses were not performed.

In addition, descriptive statistics have been used to evaluate efficacy/performance and safety variables.

SUMMARY – CONCLUSIONS

EFFICACY/PERFORMANCE RESULTS:

Primary efficacy/performance

The weekly mean TVRSS decreased significantly more from baseline to Week 4 in the Active group as compared to Placebo in the FAS population (p=0.0531). The difference between treatments in LS mean change was -0.421 (CI: -0.848 to 0.006). The significant result for the FAS was supported by the difference detected for the PPAS (p=0.0349).

Statistically significant differences between Active and Placebo in change from baseline to Week 4 in weekly mean TVRSS were found in the following sub-groups:

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- Females (p=0.0471); the difference between treatments in LS mean change was -0.710 (CI: -1.411 to -0.009).
- Age group 50 -65 years (p=0.0515); the difference between treatments in LS mean change was -0.625 (CI: -1.254 to 0.004).
- Non-allergic rhinitis (p=0.0213); The TVRSS score decreased more after active treatment as compared to Placebo; the difference in LS mean change was -0.561 (CI: -1.038 to -0.085).

Secondary efficacy/performance

TVRSS at Weeks 8-24

The improvement of weekly mean TVRSS from baseline to Week 8 was significantly better after two active treatments as compared to one active treatment (p=0.0109). The difference between treatments in LS mean change was -0.635 (CI: -1.122 to -0.148). Similar results were obtained for the PPAS population with a statistically significant difference between treatment groups at Week 8 (p=0.0190).

Individual symptom score

A significantly better improvement (more subjects shifting to a lower score) after active treatment as compared to Placebo, based on weekly median symptom scores, was seen at Week 4 for the nasal congestion symptom score (odds ratio 2.49 [CI: 1.29 to 4.82], p=0.0056). Two active treatments had a better effect on postnasal drip symptom score at Week 8 (odds ratio 2.16 [CI: 1.08 to 4.30], p=0.0271), as compared to one active treatment. At Week 24, a significantly higher proportion of subjects reported improvement of rhinorrhea symptom score after one active treatment, as compared to two active treatments (odds ratio 0.46 [CI: 0.21 to 1.01], p=0.0488).

PNIF

Based on descriptive analysis of mean PNIF values, no major difference was seen in change from baseline to Week 8. The mean increase from baseline to Week 24 was slightly higher among subjects receiving one active treatment only; 16.42 ± 46.83 L/min (median 10.00), as compared to 5.59 ± 40.71 L/min (median 7.50) after two active treatments.

SNOT-22

Based on descriptive analysis of SNOT-22 summary score, the subjects given active treatment improved more than subjects given Placebo from baseline to Week 4. The mean change from baseline to Week 4 was -8.25 ± 15.60 (median -7.00) in the Active group and -2.78 ± 12.96 (median -1.00) among subjects treated with Placebo. Subjects treated with two active treatments had a higher reduction in SNOT-22 summary score at Week 8 as compared to subjects given one active treatment. The mean change from baseline to Week 8 was -12.33 ± 14.22 (median -10.00) in the two active treatment group and -6.84 ± 14.88 (median -4.00) among subjects treated with one active treatment.

For 19/22 items, a higher percentage of subjects experienced improvement of symptoms at Week 4 after active treatment, as compared to Placebo. A higher percentage of subjects treated with Placebo experienced worsening of symptoms, as compared to active treatment, for 19/22 items. Improvement was seen in a higher percentage of subjects after two active treatments for 17/22 items at Week 8 and for 8/22 items at

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Week 24. Worsening of symptoms was reported by more subjects after one active treatment for 20/22 items at Week 8 and for 12/22 items. "*Blockage/congestion of nose*" and "*Need to blow nose"* were the two items most frequently assessed as one of the five most significant problems in all treatment groups at all time-points.

EQ-5D-3L

Based on descriptive analysis, an improvement of "*Pain/discomfort*" and "*Anxiety/Depression*" from baseline to Week 4 was experienced by a higher percentage of subjects after active treatment, as compared to Placebo. "*Pain/discomfort"* seemed to improve more frequently after two active treatments at Week 8 and after one active treatment at Week 24. A higher percentage of subjects experienced improvement of "*Anxiety/Depression*" after two active treatments at Weeks 8 and 24. No notable changes from baseline to Weeks 4, 8 or 24 in EQ Visual Analogue Scale (VAS) were seen for any of the groups.

Use of rescue medication

The mean number of days with rescue medication was similar in both treatment groups at baseline (0.7 days (CI: 0.3 to 1.1)/0.8 days [CI: 0.4 to 1.2]; Active/Placebo). During the 4 weeks following the first treatment the mean number of days with rescue medication was slightly increased in both groups (2.4 days [CI: 1.0 to 3.7] /2.8 days [CI: 1.4 to 4.3]; Active/Placebo). During the 4 weeks following the second treatment the mean number of days was somewhat higher in the One Active treatment group (2.4 days [CI: 0.9 to 3.9]) as compared to the Two Active group (1.6 days [CI: 0.4 to 2.8]).

SAFETY RESULTS:

The total number of Adverse Events (AEs) during the investigation was 226 events experienced by 120 subjects (58%), whereof 21 events, reported by 20 subjects (9.7%), were assessed as being related to the investigational procedure. Eleven (11) of these procedure-related events were also assessed as being related to the investigational device. A higher number of AEs occurred after treatment with Placebo as compared to active treatment and Low amplitude control after the first treatment. During the period following the second treatment (active treatment given to all subjects), more AEs occurred in the Placebo + Active group as compared to the two other groups (Low amplitude control + Active and Active + Active). A majority of AEs were assessed as not related to the investigational device or to clinical investigational procedures in all treatment groups. One Serious Adverse Event (SAE) assessed as not related to the investigational device or procedures, occurred in the Low amplitude control group after the first treatment.

Anticipated AEs showed to be more frequently reported in relation to active treatment as compared to the Low amplitude control and Placebo with *Increased tear secretion*, *Increased nasal secretion* and *Slight discomfort* being the most frequently reported events.

CONCLUSION:

To conclude, the present investigation demonstrated that the PBASE system was more efficacious than Placebo in reducing the weekly mean TVRSS in patients with idiopathic rhinitis. The statistical analyses showed significant differences between active treatment and Placebo regarding the primary efficacy/performance endpoint and for some of the secondary endpoints based on TVRSS. There were no concerns regarding safety in relation to treatment with the PBASE device in patients with idiopathic rhinitis.

3 TABLE OF CONTENTS

3.1 List of Tables

3.2 List of Figures

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation, acronym or specialist term	Explanation
ADE	Adverse Device Effect
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical classification system
CE	Conformité Européenne
CIP	Clinical Investigation Plan
CRF	Case Report Form
e-CRF	Electronic CRF
EEA	European Economic Association
EQ-5D-3L	EuroQol 5D-3L
FAS	Full Analysis Set
EU	European Union
IB	Investigator's Brochure
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFU	Instructions For Use
IRB	Institutional Review Board
ISO	International Standard Organisation
LS mean	Least square mean
MEDDEV	Medical Devices guidance documents
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Medical Products Agency
PCG	Pharma Consulting Group
PNIF	Peak Nasal Inspiratory Flow
PPAS	Per Protocol Analysis Set
PT	Preferred Term

Abbreviation, acronym or specialist term	Explanation
RAST	Radioallergosorbent test
SAP	Statistical Analysis Plan
SD	Standard deviation
SDV	Source Data Verification
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNOT-22	Sino-Nasal Outcome Test 22
SOC	System Organ Class
SOP	Standard Operating Procedures
TVRSS	Total Vasomotor Rhinitis Symptom Score
VAS	Visual Analogue Scale
WHO	World Health Organization

5 ETHICS AND REGULATORY

5.1 Independent ethics committee (IEC)

The final Clinical Investigation Plan (CIP) together with the final version of the Subject Information and Consent Form were approved by the Regional IEC in Stockholm on 2013-03-20, before enrolment of any subject into the investigation. The Principal Investigators were responsible for informing the IEC of any amendment made to the CIP as per local requirements (see section 9.8).

5.2 Ethical conduct of the investigation

The clinical investigation was conducted in compliance with applicable regulatory requirements and with the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association (Appendix 16.1 to the CIP, see Appendix 16.1.1 to this report).

5.3 Subject information and consent

All subjects received written and verbal information regarding the investigation prior to performing any investigation-related procedures. The subjects were informed that the participation in the investigation was voluntary and that the subject had the right to withdraw participation at any time and for any reason. All subjects were given the opportunity to ask questions about the investigation and were given sufficient time to consider participation before consenting.

Before any clinical investigation-related procedures were undertaken, the Informed Consent Form was signed and dated by the subject (or their legally acceptable representative and/or witness, as applicable) and by the Principal Investigator, or the qualified designee who gave the subject the verbal and written information.

A copy of the Subject Information and Informed Consent form, approved by the IEC is provided in Appendix 16.1.3.

5.4 Subject Data Protection

The written Subject Information explained that the data would be stored in a computer database, maintaining confidentiality in accordance with national data legislation, and that authorized representatives of the research institution, Sponsor, regulatory authorities or an IEC might require direct access to those parts of the medical records relevant to the clinical investigation, including medical history, for verification of data and appropriate conduct of the clinical investigation.

The Informed Consent Form specified that data might be transferred to European Economic Association (EEA) countries outside Sweden. In accordance with the European Union (EU) Data Protection Directive (95/46/EC), the data would not identify any persons taking part in the clinical investigation.

5.5 Regulatory Requirements

The PBASE system used in this clinical investigation is CE-marked for use in patients with non-allergic rhinitis. Therefore, an application to the Swedish Medical Products Agency (MPA) for approval in Sweden was not required.

6 INVESTIGATORS AND ADMINISTRATIVE STRUCTURE OF THE INVESTIGATION

The investigational medical device was provided by Chordate Medical, the Sponsor for this investigation.

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Subjects were recruited and treated at the following six investigational sites:

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[2] This site was replacing the former Site 004 in the revised CIP version B (see section 9.8.1.1).

[3] This site was approved by the IEC in Stockholm on 2013-09-10 (see section 9.8.2).

7 INTRODUCTION

Nasal obstruction is a very common disorder which can be caused by both anatomical and mucosal reasons. In the case of anatomical reasons septal deviation and other skeletal defects are causative. Mucosal disorders are due to a lot of underlying diseases like infections, allergic rhinitis, occupational rhinitis, hormones, drugs and iatrogenic mechanisms (1). However, in many cases no causative explanation can be found to nasal blockage and/or secretion and in these cases the terminology of idiopathic rhinitis is used as diagnose. In epidemiologic studies as much as 10-20 % of the population is found to fulfil these criteria of idiopathic rhinitis, i.e.no causative reason is found to the complaints although a thorough examination, sometimes also called “non-allergic non-infectious rhinitis” or “vaso-motor rhinitis” (2, 3). The most prominent symptom is nasal blockage but in some patients nasal hyper secretion is dominating. Histamine related symptoms like itching and sneezing are not seen. However, effects on quality of life can be very substantial (4, 5) and treatment is mostly difficult to make successful although local corticosteroids can give relief to nasal blockage in idiopathic rhinitis (6). Poor results in the treatment may be due to a multiple related aetiology of idiopathic rhinitis. Due to a lack of reliable immunological markers the role of the nerve system in the nasal cavity is of interest. Mechanisms behind the disease is thus to some extent obscure even if we know that there is some sort of imbalance in the neural regulation of the mucosal lining of the nose. The balance between sympatic and parasympatic control of the vessels and thereby an imbalance of the degree of nasal blockage is the ground for the term of “vaso motor rhinitis”. Probably, interactions between the immune system and the nerve system contribute to nasal diseases therefore the activity of the nerve system is interesting in patients with idiopathic rhinitis.

The PBASE System is a medical device used to administer pressure stimulation in the nasal cavity. It is CE marked for the treatment of non-allergic rhinitis. To influence the mucosa and nerves within the nasal cavity the device was constructed allowing time controlled kinetic oscillation stimulation by low frequency and low amplitude pressure oscillations to be delivered by the part of the device inserted in the nasal cavity. Exploratory treatment of patients with different conditions of other kinds has been tested in small cohorts with in many cases promising results in terms of reduction in disease activity without safety concerns. The aim of this double-blinded, placebo-controlled, parallel-group investigation was to investigate if kinetic oscillation stimulation applied to the nasal mucosa surface for several minutes, can reduce rhinitis symptoms in patients with idiopathic rhinitis.

8 OBJECTIVES

8.1 Primary objectives

The primary objective was to evaluate the performance of the PBASE system, in terms of the efficacy of treatment with the device upon Total Vasomotor Rhinitis Symptom Score (TVRSS).

8.2 Secondary objectives

The secondary objectives were:

a) To evaluate the efficacy on individual nasal symptom scores and Peak Nasal Inspiratory Flow (PNIF)

b) To evaluate the efficacy on health related quality of life

c) To evaluate the safety of the PBASE system

9 INVESTIGATIONAL DEVICE AND METHODS

9.1 Investigational device description

9.1.1 Identification of the Clinical Investigational Medical Device and Control

The clinical investigational medical device was the PBASE system. The PBASE System 1.1 consists of a base unit (PBASE Device 1.1 and Power Supply) and an associated balloon (Catheter A100). The PBASE Device 1.1 and Catheter A100 cannot be used separately. A BALL Fixation Device is used in conjunction to form a complete and useful system. In this investigation, a placebo module CT100 was used in combination with the PBASE system and the BALL Fixation Device.

Full details are found within the Instructions for Use (IFU), Ref no 1001331, appended to the Investigator's Brochure (IB) (7). The IFU is appended to this report as Appendix 16.1.2.

9.1.1.1 PBASE Device 1.1

The PBASE Device 1.1 (Ref no 1001337) is intended to create air mediated oscillations with controlled pressure and frequency for a predetermined treatment time. It is the base unit creating vibrations (Figure 9.1 and Figure 9.2). The front displays the parameters values used, frequency, pressure and time. PBASE Device 1.1 consists of a mechanical pneumatics part (pumps, valves, tubings), an electronic microcontroller part (MCU, motor drives, pressure gauge), and a user control panel (LED display, push buttons).

For this investigation, the system was set at parameters used for treatment of rhinitis (see section 9.1.4.2). The parameter values were shown on the user panel. When the user pressed the start button an automated treatment sequence started. The subject treated and equipment were never left without supervision during treatment and the operator could pause and cancel the treatment at any time.

Figure 9.1 PBASE Device 1.1 Front View

Figure 9.2 PBASE Device 1.1 Back View

Supplied with:

- Mean Well MES50A-6P1J Medical Power Adaptor (Ref no 1001155) below referred to as Power Supply
- Power cord

9.1.1.2 Catheter A100

Catheter A100 (Ref no 1001245) (Figure 9.3) is a single-subject, single-occasion use product that is partly inserted in to the nasal cavity of the subject, transferring the low frequency oscillations generated by PBASE Device 1.1. Before use, Catheter A100 is connected to PBASE Device 1.1 via the placebo module CT100 and the balloon part is inserted in to the nasal cavity of the subject. When started, the Catheter A100 is inflated and the oscillations will be transferred on to the mucosal membranes of the nasal cavity. A gel of medicinal liquid paraffin is put on the balloon before use.

Catheter A100 consists of the following parts:

- Balloon made from polyvinylchloride
- Plastic cable in two sizes
- Plastic adapter that connects Catheter A100 to Placebo module CT100
- Cable tie

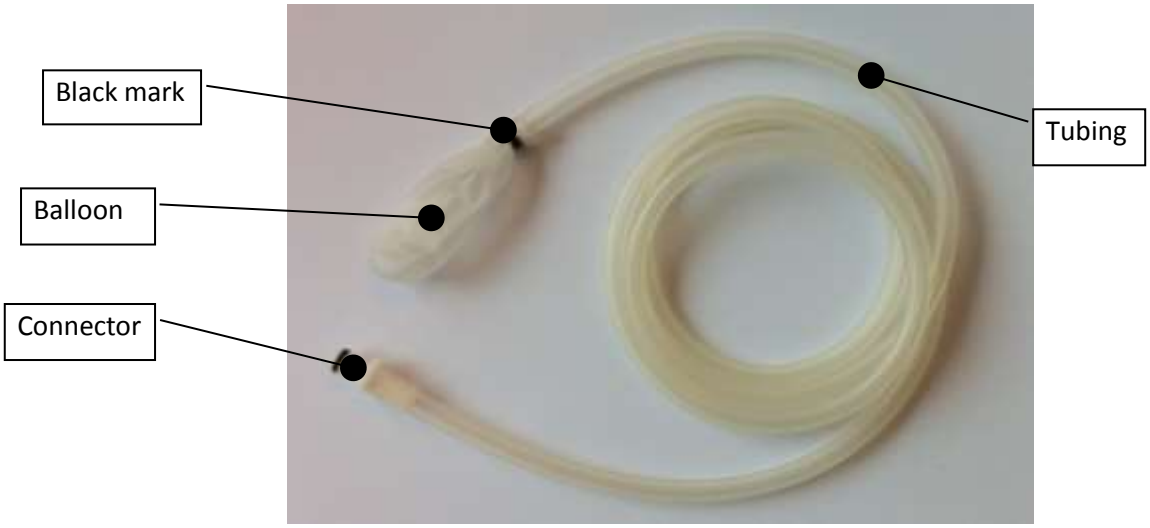


Figure 9.3 Catheter A100

9.1.1.3 Placebo module CT100

The placebo module CT100 was developed to be able to conduct double blind placebo controlled clinical investigations.

Placebo module CT100 (reference number 1001341) was placed between PBASE Device 1.1 and catheter A100. CT100 had one input connected to the output of PBASE 1.1 and six outputs (A-F) where one Catheter A100 was connected. Three outputs delivered active treatment and three outputs delivered control treatment . The operator selected the output according to the randomization code generated in the electronic Case Report Form (e-CRF), Viedoc™, and blinded treatment was administered.

Figure 9.4 Placebo module CT100

9.1.1.4 BALL Fixation Device

The BALL Fixation Device (Ref no 1001152) (Figure 9.5) is intended for multi-subject use in a clinical environment, to fixate the Balloon catheter, during treatments in the nasal cavity. To reduce the risk of contamination between subjects disposable hair nets are used.

The BALL fixation device consists of head-band, link-arm, and clips. The head-band was placed on the head of the subject, Catheter A100 was inserted as intended use, the clips connected to the tubing on Catheter A100 and link-arm was locked.

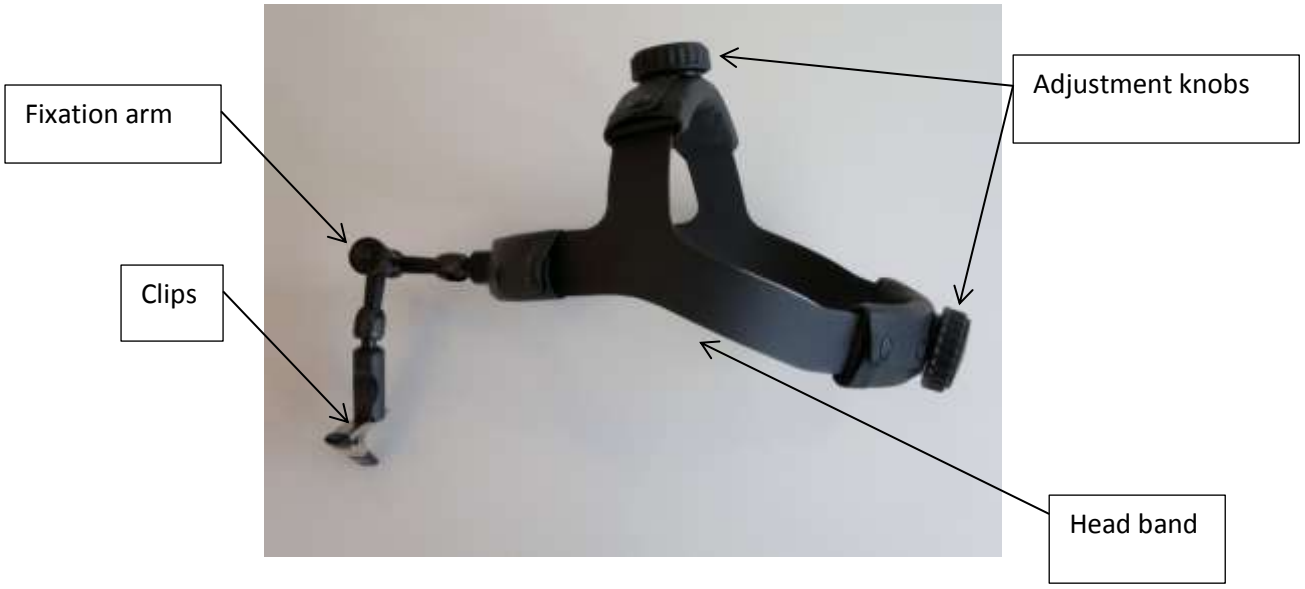


Figure 9.5 BALL Fixation Device

9.1.1.5 Other devices/products used with the PBASE system

In addition to the PBASE system, BALL Fixation Device and the Placebo module CT100, delivered by Chordate Medical, the user needed to use the following:

- Medicinal liquid paraffin
- Hair nets (as pictured in Figure 9.6).

9.1.2 Intended use

The PBASE system is used to stimulate human tissue inside the nasal cavities by means of mechanical pressure and oscillations at low frequencies. The device is an active therapeutic device intended to administer energy. The system is intended to be used by healthcare professionals in a clinical environment. It is CE marked for the treatment of non-allergic rhinitis. The aim of this investigation was to investigate if kinetic oscillation stimulation applied to the nasal mucosa surface for several minutes, could reduce rhinitis symptoms in patients with idiopathic rhinitis.

9.1.3 Installation and Use of the Clinical Investigational Medical Device and Control

The investigational device was used (including set-up and storage) as per the instructions contained within the IB and IFU. Detailed information regarding installation and handling of the device as well as storage and operating technical information is available in section 8.5.3 of the CIP (see Appendix 16.1.1 to this report).

9.1.4 Treatment procedure

Treatment was administered by a doctor or nurse trained in the PBASE system treatment procedure. In addition to the brief instructions below, the IFU contained safety instructions to be observed. The Catheter A100 was a single-use device, i.e. the device could be used to treat both nostrils of the same subject but was not to be used on more than one subject.

9.1.4.1 Conducting a Treatment

a. The subject was allowed to sit in an upright position in the treatment chair.

b. Passage between inferior turbinate and nasal septum was confirmed during the screening visit (Visit 1) to avoid a pronounced anterior septal deviation.

c. The protection hair net was placed on the subject's head.

d. The BALL Fixation Device was placed on the subject's head. Knobs were used at top and rear of the device to adjust for fit and comfort. Bottom of headband should be even with top of ears (see Figure 9.6). It was made sure that the fixation arm or clip did not accidentally fall into the face of the subject.

e. The balloon part of the unused Catheter A100 was squeezed to ensure that any air was evacuated.

f. Three (3) cm of the balloon part of the unused Catheter A100 was dipped into medicinal liquid paraffin.

g. The balloon was inserted into the subject's nostril (either side) following along the superior aspect of the hard palate, until the black mark was 0-5mm outside the nostril. The balloon was not to be rotated during insertion (see Figure 9.7).

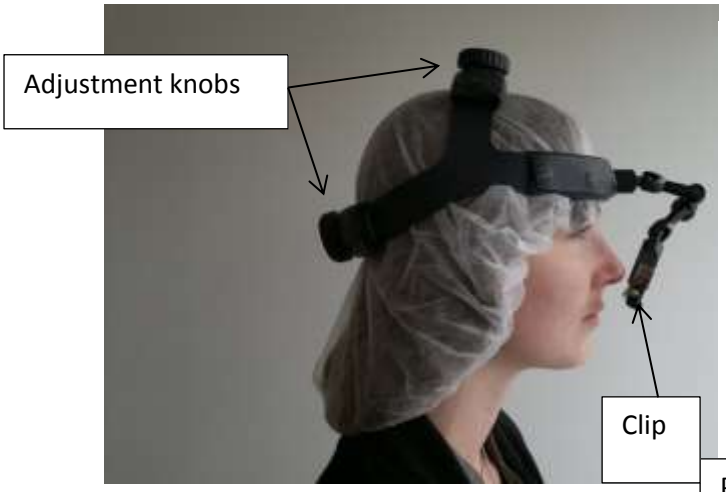
h. The position of the fixation arm was adjusted to maintain the catheter in a comfortable and proper position. The catheter tubing was connected to the clamp on the BALL Fixation Device, making sure that the clamp was placed as close to the black mark as possible, see Figure 9.7.

i. The treatment was started by pressing the "START/PAUSE" button once. The PBASE Device automatically inflated the catheter to the correct pressure and the treatment started after a short delay.

j. The treatment was completed when the treatment time had elapsed. The oscillations were stopped and the system was vented automatically at completion of the treatment.

k. The deflated balloon was extracted from the nasal cavity.

The treatment was repeated in the other nasal cavity by performing steps **e, and g through k** once more. Step **f** only applied to the first nostril (or when a new unused Catheter A100 was used). The balloon part of a used Catheter A100 was never to be dipped in the medicinal liquid paraffin bottle.



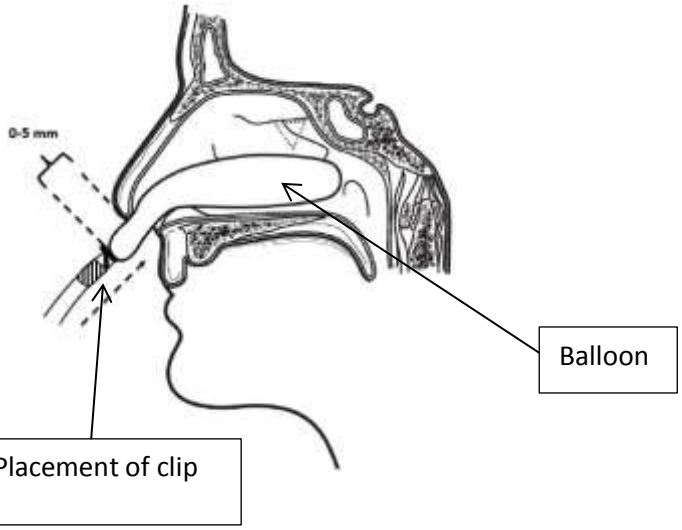


Figure 9.6 - Placement of BALL Fixation Device

Figure 9.7 - Placement of balloon during treatment

9.1.4.2 Treatment Protocol

The pre-set frequency (fixed value of 68 Hz) and pressure (fixed value of 65 millibar [mbar]) was used in the treatment of all subjects. The Low amplitude control differed from the active treatment by giving much lower amplitude of the kinetic oscillations.

All subjects received the pre-set 10 minutes of continuous treatment time per nostril. Once one nostril had been treated, the doctor/nurse treated the opposite nostril with a minimum of delay.

Ten (10) continuous minutes per nostril with a maximum of 5 minutes break between nostrils had been determined as the optimum rhinitis treatment protocol and Investigators were instructed to adhere to this wherever possible.

However, if one or more breaks in treatment could not be avoided or treatment could not be maintained for the correct period of time, scenarios meeting all of the following criteria would not be classified as deviations:

- Total treatment time for both nostrils was between 15 and 20 minutes;
- Total treatment time plus total break time ≤ 30 minutes;
- Total break time ≤ 10 minutes.

Any deviations from the treatment protocol or the IFU were to be recorded in the e-CRF.

9.1.5 Subject identification

Eligible and consenting subjects were allocated the next available screening number automatically generated by the e-CRF system (Viedoc™). All subjects randomized were given a subject number in consecutive order. The subject was identified by the screening and subject numbers throughout the investigation. The following number serials were allocated to the different sites:

Site No.	Screening numbers	Subject numbers
001	SE101-199	101-199
002	SE201-299	201-299
003	SE301-399	301-399
004	SE401-499	401-499
005	SE501-599	501-599
006	SE601-699	601-699

9.1.6 Method of Assigning subjects to Treatment Groups

At the first treatment visit (Visit 2) each subject was randomized to either active treatment or control treatment. At the second treatment visit (Visit 3) all subjects received active treatment but randomization was performed for blinding purposes.

Randomization was performed in the e-CRF, Viedoc™, by allocating the subject to a randomization letter (A, B, C, D, E or F). The randomization letter was linked to a specific connector on the CT100 module corresponding to either control or active treatment. Three connectors delivered active treatment and three delivered control treatment.

The randomization code was broken after clean file had been declared.

9.1.7 Blinding

Neither the subject nor the treatment operator knew what specific treatment was assigned during the first treatment visit. The blinding was kept by randomly allocating active treatment from one of three connectors on the CT100 module at Visit 3, although all subjects received active treatment.

The interim analyses were performed by one project statistician. The project statistician performing the interim analyses was not involved in decisions regarding data handling and definitions of analysis populations taken before the code was broken and clean file was declared. To avoid bias in the treatment of patients during the investigation, the interim results were not distributed to participating clinical staff members. The results from the interim analyses were stored in locked folders with access for the project statistician performing the interim analyses only.

9.1.8 Rescue medication

Subjects were allowed to use Rinexin® whenever they considered this to be necessary to relieve their rhinitis symptoms. However, all such use was reported in the electronic subject diary on a daily basis. Subjects suffering from rhinitis medicamentosa were advised to stop using nose drops after the first treatment visit (Visit 2) up to study completion.

9.1.9 Prior and Concomitant Therapy

As no interactions were anticipated between treatment with the investigational device and concomitant medications, the only restrictions for concomitant medications were related to those which could potentially affect interpretation of the results. Therefore, subjects with ongoing treatments for respiratory tract infections were not to be enrolled. Subjects using concomitant medications (other than the rescue medication) for rhinitis, e.g. nasal steroids, were advised to remain on stable dose (no change in amount, dose or brand) from the screening visit up to the end of

participation in the investigation. All changes in concomitant therapy were reported in the subject diary.

Medication considered necessary for the subject's safety and well-being could be given at the discretion of the Principal Investigator at any time. The Investigator recorded the concomitant medication information in the appropriate section of the e-CRF.

In terms of procedures, subjects were not to be included if they were implanted with an electrical and/or neuro-stimulator device at the time of enrolment, including but not limited to cardiac pacemaker, defibrillator, vagal neuro-stimulator, deep brain stimulation, spinal stimulator, bone growth stimulator, or cochlear implant or any other implant in the head-, and neck region. In addition, subjects who had previously received treatment with radiation to the face, head or neck regions, had undergone any nasal surgery except from closed nasal reposition, or had pronounced anterior septal deviation or other significant nasal pathology were not to be included in this clinical investigation. These exclusion criteria were based on the results of the risk analysis, detailed in the Risk Assessment of Kinetic Oscillation Stimulation Treatment (ref 1001159) and included in the IB (7).

9.1.10 Compliance with device usage

The investigational devices were only to be used as part of the clinical investigation according to the CIP and manufacturer's IFU. The device was supplied to the Principal Investigator with pre-set algorithms to be used for this specific investigation. Any deviations to the prescribed technique and timing were recorded.

9.1.11 Accountability/traceability of devices

Receipt and return of the clinical investigational devices were tracked and documented by the Monitor and Principal Investigator. Product name, amount, batch number and any applicable expiry dates were documented for investigational devices provided. The investigational devices were returned to the Sponsor at the end of the investigation.

9.2 Clinical investigational plan (CIP)

This was an interventional, double-blinded, placebo-controlled, multi-centre investigation in which subjects diagnosed with idiopathic rhinitis and fulfilling the inclusion/exclusion criteria received intranasal stimulation with the PBASE system on at least one occasion. The objectives were to evaluate the efficacy/performance of the procedure in reducing disease specific symptoms such as nasal congestion, rhinorrhea, postnasal drip and sneezing, but also to investigate the influence on quality of life, safety and tolerability. The planned number of investigational subjects was 158, 79 in each treatment group.

A planned interim analysis with the aim to achieve safety and efficacy/performance interim data to be used for strategy and design of future studies was performed when 97 subjects had completed Visit 3 (Week 4), 48 randomized to Low amplitude control and 49 to active treatment. Based on this interim analysis the sample size was recalculated (see section 9.8.1.3) and the control treatment was modified (Placebo) according to section 9.8.1.2. The total number of subjects to be randomized was revised to be 208; 80 to active treatment, 79 Placebo and 48 to Low amplitude control. A second interim analysis was performed when at least 50% of the Placebo subjects were estimated to have completed Visit 3 (Week 4), as described in section 9.8.3.

The study consisted of a Screening Visit (Visit 1), two treatment visits (Visits 2 and 3) and two follow-up visits (Visits 4 and 5). In addition, a follow-up telephone call was performed in between Visit 4 and Visit 5 (see Figure 9.8).

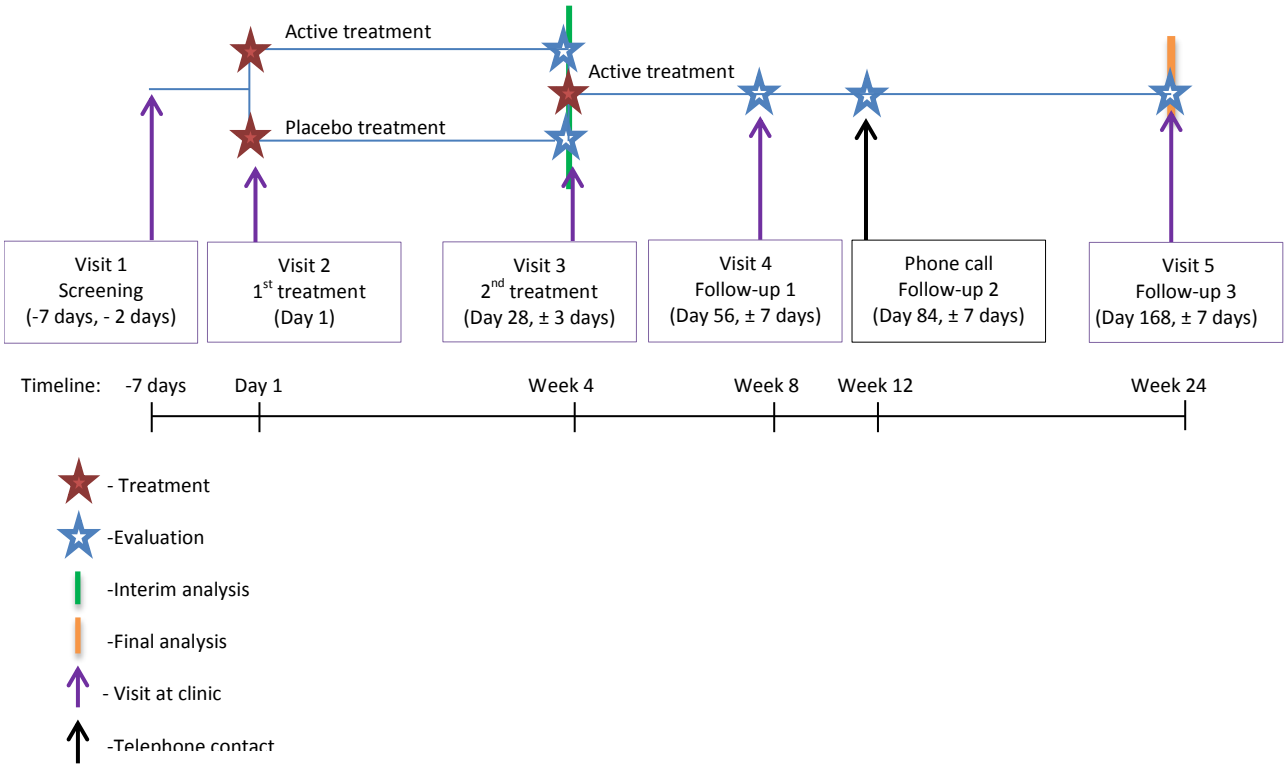


Figure 9.8 Study flow-chart

Patients diagnosed with idiopathic rhinitis were informed about the study verbally and in written before any study-specific procedures were performed. More detailed information about the informed consent process is provided in section 5.3.

Consenting subjects were allocated to the next available screening number automatically generated by the e-CRF system (Viedoc™) and were screened for eligibility at Visit 1 (Screening Visit). Assessments were performed as described in Table 9.1. Eligible subjects entered a prospective baseline period of 7 days, starting from the day following the Screening Visit. The subject was trained on the use of the electronic subject diary Viedoc Me™ (provided by PCG) by a member of the research team. The subject was asked to complete the diary on a daily basis, before 12 noon, between the Screening Visit and the Week 8 follow-up visit (Visit 4) and thereafter during the week prior to the remaining follow-up (Week 12 telephone follow-up and Visit 5; Week 24). The average intensity of nasal symptoms during the previous 24 hours, use of rescue medication and change in concomitant medications during the previous 24 hours were recorded in the diary.

The first treatment visit (Visit 2) took place within 7-9 days from Visit 1. After eligibility had been confirmed based on diary data and a pregnancy test for women of childbearing potential, eligible subjects were randomized to active treatment or to the control group (Low amplitude control/Placebo). Investigational assessments were performed according to Table 9.1 and the intranasal treatment was given according to the treatment allocation as described in section 9.1.4.

The second treatment visit (Visit 3) took place 4 weeks after Visit 2 (Day 28 ± 3 days). All subjects were given active treatment at this visit. For blinding purposes, randomization was performed and subjects were randomly allocated to one of three connectors on the investigational device delivering active treatment.

Treated subjects were followed up by telephone and visits; Week 8 follow-up (Visit 4; Day 56 ± 7 days), Week 12 (3 month) telephone follow-up (Day 84 ± 7 days), and Week 24 (6 month) follow-up (Visit 5; Day 168 ± 7 days).

The schedule of assessments performed during the investigation is displayed in Table 9.1. Each assessment and corresponding endpoints are presented in detail in section 9.5.

Table 9.1 Schedule of Events

	Screening/ Run-in *Day -9 –Day -2*	**Treatment 1** *Day 1; Week 0*	**Treatment 2** *Day 28 ± 3 days Week 4*		**Follow-up 1** *Day 56 ± 7 days Week 8*	**Follow-up 2** *Day 84 ± 7 days Week 12*	**Follow-up 3** *Day 168 ± 7 days Week 24*
Study Visits/ Contacts	**Visit 1[1] Screening**	**Visit 2**	**Visit 3**		**Visit 4**	**Telephone call**	**Visit 5**
Visit/contact type	Doctor	Nurse/Doctor	Nurse/Doctor		Nurse/Doctor	Nurse/Doctor	Doctor
Informed consent signed[2]	X						
Demographics	X						
Inclusion/Exclusion criteria	X	X					
Medical and surgical history	X						
Physical examination[3]	X						
Allergy test[4]	X						
Concomitant medication	X	X	X		X	X	X
Urine pregnancy test		X			X		
Randomization		X	X				
Treatment with PBASE system[5]		X	X				
PNIF	X	X	X		X		X
SNOT-22[6]	X		X		X		X
EQ-5D-3L+VAS[6]	X	X	X		X		X
Adverse Event (AE) review with subject[7]		X	X		X	X	X
Ad hoc AE reports by subject (as required)[7]							
Patient Diary (daily registration)							
Nasal symptom scores[8]							
Rescue medication, concomitant medications							
Patient Diary (1 week before next visit)							
Nasal symptom scores						X	X
Rescue medication, concomitant medications						X	X

INTERIM ANALYSIS

1. Screening Visit performed 7-9 days prior to first treatment visit (Visit 2). Baseline/run-in period Day -7-Day 0.
2. Must be obtained prior to initiating any study procedures
3. Physical examination including endoscopic investigation
4. Either skin prick test (Histamine (positive control), NaCl (negative control), pteronyssis (mites), farinae (mites), cladosporium (mold), alternaria (mold), dog, cat, horse, birch, timothy and mugwort), phadiatop or Radioallergosorbent test (RAST)
5. Active or Low amplitude control/Placebo treatment during 10 minutes at each side of the nose
6. Questionnaires were collected at respective visit and data transcribed into the e-CRF following the visit.
7. All reported AEs will be recorded from enrolment at first treatment visit (Visit 2) until the Week 24 follow-up visit.
8. Nasal symptoms (congestion, rhinorrhea, postnasal drip and sneezing) were evaluated using a four point categorical scale: none, mild, moderate and severe

9.3 Discussion of investigation design, including the choice of control groups

This was a clinical investigation designed to evaluate efficacy/performance of the treatment with the PBASE system on rhinitis associated symptoms and health related quality of life, in patients suffering from idiopathic rhinitis. Investigational subjects were randomized to either active or inactive treatment (Low amplitude control/Placebo) with the PBASE system at the first treatment occasion and all subjects received active treatment at the second occasion in order to investigate whether there was a significant difference between active treatment and Low amplitude control/Placebo, but also whether two active treatments caused an additive effect compared to one active treatment.

Specific subject characteristics were included with the aim of reducing variables that could influence treatment outcomes and interpretation of these. The rational for individual subjects characteristics included in the clinical investigation are detailed below:

- Non-allergic subjects with persistent (>12 w) symptoms of idiopathic rhinitis dominated by nasal congestion (± secretion) for an average of at least 1 hour per day for at least 5 days during a period of 14 days: this was a rhinitis investigation and it was important to ensure that only subjects with the target indication were enrolled.
- Nasal congestion as major symptom and a nasal congestion score of at least 2 (scale 0-3): to ensure that subjects included in the investigation were comparable and to ensure that all subjects had at least moderate nasal congestion.
- Both males and females were enrolled in order to investigate outcomes in both genders.
- The age range 18 to 65 years was defined for this clinical investigation of adult idiopathic rhinitis. Age above 65 years is sometimes associated with transformed nasal mucosa and nasal function. Furthermore, subjects older than 65 years often have higher comorbidity and concomitant medications, which can confound interpretation of treatment effects.

9.4 Selection of study population

Patients potentially suitable for participation were identified from either the Principal Investigator's current patient base or via ethically-approved patient recruitment materials. Advertisements were used at sites nos. 001, 002, 003, 004 and 006.

9.4.1 Inclusion Criteria

1. Patients with persistent (>12w) symptoms of idiopathic rhinitis dominated by nasal congestion (± secretion) for an average of at least 1 hour per day for at least 5 days during a period of 14 days.
2. Having nasal congestion as major symptom, and a nasal congestion score of at least 2 (scale 0-3).
3. Male or female 18 - 65 years.

4. Judged by the Investigator as suitable for participation in the study without safety concerns based on medical history and physical examination.
5. Willing and able to provide written informed consent prior to participation in the clinical investigation.
6. Willing and able to comply with all study related procedures.

9.4.2 Exclusion Criteria

1. Patients with allergic rhinitis, demonstrated by either positive skin prick test, phadiatop or RAST.
2. Ongoing respiratory tract infection including nasal cavity at inclusion (at first treatment visit).
3. Systemic steroid treatment less than 4 weeks before the inclusion in the study.
4. Patients with a history of nasal surgery like: septoplasty, cosmetic surgery, conchal surgery or any other nasal surgery except closed reposition for nasal fracture.
5. History of frequent nose bleeds or a condition that increases the risk of excessive bleeding.
6. Pronounced anterior septal deviation or other significant nasal pathology at endoscopic examination.
7. Current malignancy of any kind.
8. Known allergy to polyvinylchloride or medicinal liquid paraffin.
9. Any disease, condition (medical or surgical) which, in the opinion of the Investigator, might compromise the study results, or would place the subject at increased risk.
10. Any implant with an electrical and/or neurostimulator device, including but not limited to cardiac pacemaker, defibrillator, vagal neurostimulator, deep brain stimulation, spinal stimulator, bone growth stimulator, or cochlear implant or any other implant in the head-, and neck region.
11. Previous treated with radiation on the face, head or neck regions.
12. Female patients who were pregnant or nursing, or become pregnant at any time from inclusion of the study until end of the Week 8 follow-up visit.
13. Female patients: unwilling to use adequate contraceptive from the signing of the informed consent until end of the Week 8 follow-up visit
14. Received study drug in a clinical study for an investigational drug within the previous 30 days, or 5 half-lives, whichever was longer.

9.4.3 Removal of Subjects from Therapy or Assessment

Subjects were free to discontinue participation in the clinical investigation at any time, without prejudice to further treatment. Subjects who discontinued the clinical investigation were asked about the reason(s) for their discontinuation and about the presence of any Adverse Events (AEs) and were, if possible, assessed by the Principal Investigator.

Subjects could be withdrawn from investigational treatment and assessments at any time, if deemed necessary by the Principal Investigator or Sponsor.

In case of withdrawal, AEs were followed up by the Principal Investigator according to section 9.5.6.1.

9.5 Assessments and endpoints

9.5.1 Demographics

Age (recorded as date of birth), gender, height and weight were recorded at Visit 1 (screening).

9.5.2 Medical history

Relevant medical history and rhinitis history were recorded at Visit 1 (screening). Presence of allergies, pronounced septal deviation, history of nasal trauma, sense of smell, unilateral/bilateral congestion, and previous nasal surgery were recorded separately.

9.5.3 Prior and concomitant medication

Prior and concomitant medications were recorded for each subject for the duration of the clinical investigation.

9.5.4 Efficacy/performance assessments and endpoints

9.5.4.1 Total vasomotor rhinitis symptom score (TVRSS)

The average intensity of nasal symptoms during the previous 24 hours were registered by the subject in the electronic subject diary on a daily basis (before 12 noon) between the Visit 1 (baseline) and the Week 8 follow-up visit (Visit 4). After Visit 4, assessments were made only during the week prior to the remaining follow-ups (Week 12 telephone follow-up and Visit 5; Week 24).

TVRSS is the sum of the four symptom scores: nasal congestion, rhinorrhea, postnasal drip and sneezing. Each symptom score is rated on a four point categorical scale: 0=none, 1=mild, 2=moderate and 3=severe. The TVRSS ranges from 0-12 where higher scores represents poorer outcome.

The following endpoints were derived from the TVRSS assessments:

<u>Primary efficacy/performance endpoint</u>

- Change in weekly mean TVRSS from baseline to Week 4. The difference between subjects receiving active treatment (Active) at the first treatment visit and subjects receiving Placebo has been analysed.

<u>Secondary efficacy/performance endpoint</u>

- Change in weekly mean TVRSS from baseline to Weeks 8, 12 and 24. The difference between subjects receiving two active treatments (Active + Active) and subjects receiving one Placebo and one active treatment (Placebo + Active) has been analysed.

- Change in weekly median of each individual symptom score (nasal congestion, rhinorrhea, postnasal drip and sneezing) from baseline to Week 4. The difference between Active and Placebo has been analysed.
- Change in weekly median of each individual symptom score (nasal congestion, rhinorrhea, postnasal drip and sneezing) from baseline to Weeks 8, 12 and 24. The difference between two active treatments and one active treatment has been analysed.

9.5.5 Peak Nasal Inspiratory Flow (PNIF)

PNIF measurements were performed at Visit 1 (baseline), before treatment with the investigational device at Visit 2 (Week 0), at Visit 3 (Week 4) and at follow-up Visits 4 (Week 8) and 5 (Week 24). At each visit, three measurements were registered. For the analyses, the highest value of measurement no. 2 and 3 has been used (8). The first measurement was considered as a training measurement.

The following endpoints were derived from the PNIF measurements:

- Change from baseline to Week 4 (presented descriptively by treatment; Active/ Placebo).
- Change from baseline to Weeks 8 and 24 (presented descriptively by treatment group; Two Active/ One Active).

9.5.5.1 Rhinosinusitis-specific quality of life, according to the Sino-Nasal Outcome Test 22 (SNOT-22) questionnaire

The SNOT-22 questionnaire was completed by the subject at Visit 1 (baseline) before treatment with the investigational device at Visit 3 (Week 4) and at follow-up Visits 4 (Week 8) and 5 (Week 24). The questionnaire was transcribed into the e-CRF by the Investigator/study staff following the visit.

The SNOT-22 is a self-report questionnaire for use as a measure of health outcome in patients suffering from rhinosinusitis conditions. It is a descriptive system consisting of 22 questions with six response options. The responses record 6 levels of severity (NO PROBLEMS/MINIMAL PROBLEMS/MILD PROBLEMS/MODERATE PROBLEMS/SEVERE PROBLEMS/WORST IMAGINABLE PROBLEMS).

The SNOT-22 is simple for subjects to complete and should take less than five minutes.

A SNOT-22 summary score ranging from 0-110 was calculated. Higher scores represents poorer outcome.

The following endpoints were derived from the SNOT-22 questionnaire:

- Change in SNOT-22 summary score from baseline to Week 4 (presented descriptively by treatment; Active/Placebo).
- Change in SNOT-22 summary score from baseline to Weeks 8 and 24 (presented descriptively by treatment group; Two Active/ One Active).

9.5.5.2 Functional disability and health-related quality of life, according to the EuroQol-5D-3L (EQ-5D-3L) questionnaire

The EQ-5D-3L questionnaire was completed by the subject at Visit 1 (baseline), before treatment with the investigational device at Visit 2 (Week 0), Visit 3 (Week 4) and at follow-up Visits 4 (Week 8) and 5 (Week 24). The questionnaire was transcribed into the e-CRF by the Investigator/study staff following the visit.

The EQ-5D-3L is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status (9). The EQ-5D-3L is extensively validated, sensitive to small changes in quality of life, and is being increasingly used by healthcare purchasers and policy makers in the clinical and economical evaluation of healthcare.

The EQ-5D-3L self-report questionnaire consists of the EQ-5D-3L descriptive system and the EQ VAS. The EQ-5D-3L is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of three responses. The responses record three levels of severity (no problems/some or moderate problems/extreme problems) within a particular EQ-5D-3L dimension. The EQ VAS is a standard vertical 20 cm visual analogue scale (similar to a thermometer) for recording an individual's rating of their current health-related quality of life state (9). The end points of the scale are labelled "BEST IMAGINABLE HEALTH" state at the top (100) and "WORST IMAGINABLE HEALTH STATE" at the bottom (0).

With only six questions, the EQ-5D-3L is simple for subjects to complete and should take less than three minutes.

The following endpoints were derived from the EQ-5D-3L questionnaire:

- Change in EQ-5D-3L score from baseline to Week 4 (presented descriptively by treatment; Active/Placebo).
- Change in EQ-5D-3L score from baseline to Weeks 8 and 24 (presented descriptively by treatment group; Two Active/ One Active).

9.5.5.3 Use of rescue medication

The use of the rescue medication Rinexin® was registered by the subject on an ongoing basis in the subject diary.

Number of days with rescue medication will be presented descriptively by visit.

9.5.6 Safety assessments and endpoints

9.5.6.1 Adverse Events (AEs) and Device deficiencies

All subjects were carefully monitored for the occurrence of AEs during the clinical investigation period. All AEs, except for anticipated device effects of mild character, were to be recorded in the CRF and evaluated by the Investigator (severity, causality and seriousness). All AEs were automatically notified to the Sponsor upon data entry by the site personnel into the e-CRF.

Any AE ongoing when the subject was withdrawn from the investigation was followed until the AE had resolved or stabilized, as judged by the Investigator. The date when the Investigator considered one of these outcomes to have occurred for the last ongoing AE for a subject was considered the last visit for this subject, and the outcome was recorded in the e-CRF.

Serious Adverse Events (SAEs)/Serious Adverse Device Effects (SADEs) were to be reported to the Sponsor within 24 hours of learning about the event, regardless of the time that had elapsed from the time the event occurred. All SAEs had to be reported, whether or not they were considered causally related to the investigational medical device, according to the instructions given in the CIP.

All AEs meeting the definition of serious were immediately flagged to the Sponsor by the e-CRF system upon data entry by site personnel. SAE report data were signed-off in the e-CRF by the Principal Investigator.

The Sponsor informed the IEC about SAEs and SADEs associated with the use of the device according to Medical Devices guidance document (MEDDEV) 2.7/3.

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device (including malfunctions, use errors, and inadequate labelling) were to be documented.

For detailed definitions and reporting procedures, see CIP (Appendix 16.1.1 to this report).

9.5.7 Appropriateness of Measurements

Rhinitis symptoms impact on patients' daily functioning and quality of life. The efficacy/performance endpoints, and associated variables and measurements used, are consequently subject self-reported and reflect these elements. The TVRSS has been used in other clinical investigations on idiopathic rhinitis and was believed to be clinically relevant.

The use of simple subject diaries to record rhinitis details was necessary to gather longer-term baseline and treatment outcome data.

A combination of AE review and ad hoc subject AE reporting ensured an accurate representation of AE's occurring during the clinical investigation.

9.6 Data quality assurance

The clinical investigation data were collected in an e-CRF completed by the Principal Investigator, or other qualified site personnel and by online diaries completed by the subject. Together these constituted a remote electronic data system, compliant with the associated requirements of EN International Standard Organisation (ISO) 14155:2011(10).

The 21 CFR Part 11-compliant e-CRF (Viedoc™) used was provided by PCG and included password protection with unique user IDs and internal quality checks. Clinical data were entered directly from the source documents, unless the e-CRF was considered source, by authorized investigational site personnel designated by the Principal Investigator. Appropriate training and security measures were completed with the Principal Investigator and all authorized site personnel prior to initiation of the investigation and any subject data being entered into the system. The Principal Investigator was required to electronically sign off all clinical data entered.

All changes made in the e-CRF were fully recorded in a protected audit trail, and a reason for the change was documented. Once all data had been entered, verified, and validated, the database was locked according to PCG Standard Operating Procedures (SOPs).

The study sites were periodically visited by a Monitor from Chordate Medical. The Monitor had direct access to medical records and verification of data entered into the e-CRF against source data was performed (Source Data Verification [SDV]). The e-CRFs were reviewed and evaluated for completeness and consistency.

All site personnel involved in the study were listed on a Delegation Log kept and updated by the Principal Investigator.

Before inclusion of subjects into the investigation, an initiation visit was performed by the Monitor at each site in order to inform and train relevant study staff. The Investigator was thereafter responsible for providing appropriate study related training to new staff and to forward any new information of relevance to the performance of this investigation to the staff involved.

9.7 Statistical methods planned in the CIP and determination of sample size

9.7.1 Statistical and Analytical Plans

A more detailed description of the statistical methodology is presented in the Statistical Analysis Plan (SAP), included as Appendix 16.1.7.

9.7.1.1 General

In the efficacy/performance analyses the main comparisons have been made between active treatment and Placebo. For the Low amplitude control group only summary statistics of efficacy/performance will be produced.[4]

Continuous data are presented with the number of observations, mean value, standard deviation, minimum, Q1, median, Q3 and maximum value. Categorical data are presented as counts and percentages. The data are presented for each visit or for pre-defined time periods as described below and summarized by treatment group; Active, Placebo and Low amplitude control.

Generally, a baseline measurement refers to the last non-missing assessment made before treatment start.[5]

9.7.1.2 Analysis data sets

The following analysis sets have been used for the statistical analysis and presentation of data:

The Full Analysis Set (FAS) is defined as all treated subjects with baseline data and any post baseline data.

The Per Protocol Analysis Set (PPAS) includes subjects who fulfil the following criteria:

- Included in the FAS.
- Do not have any other major CIP violations which will affect the assessment of efficacy/performance. An example of a major CIP violation is a subject who terminated the study participation before the primary endpoint follow-up or violation of the inclusion/exclusion criteria.
- Have available primary endpoint data
- Have full duration of study treatment.

The safety analysis set consists of all subjects treated (at least once).

The baseline and safety presentations will be based on the safety analysis set.

The FAS is considered as the primary analysis dataset, and has been used for all primary and secondary performance analyses. The PPAS has been used for the efficacy/performance analysis to investigate the sensitivity of the results from the FAS analysis (for TVRSS data only).

Subjects screened but not included in the study have only been presented in a table summarizing the disposition of subjects.

[4] The modified control arm (Placebo) was introduced in the revised CIP dated 2013-07-15. The revision was made after the interim analysis and the changes are described in detail in section 9.8.

[5] For exceptions from this general rule, see section 9.8.3.

9.7.1.3 Demographic and Other Baseline Characteristics

Subject disposition, demographics and other baseline data are presented using summary statistics.

9.7.1.4 Medical history and concurrent diseases

Medical history ("History") and concurrent diseases ("Ongoing") have been coded by System Organ Class (SOC) and Preferred Term (PT) by qualified staff at PCG using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 and is presented as number and percentage of subjects in each SOC and PT.

Subjects dependent on sympathomimetic drugs for satisfying nasal breathing and who used these types of drug(s) on a regular basis have been considered rhinitis medicamentosa patients in this study.

9.7.1.5 Prior and Concomitant Medication

Medications have been coded by qualified staff at PCG using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system, version Jan-2013. The number and percentage of subjects and number of mentions in each ATC Level 2 (therapeutic main group) and Level 5 (chemical substance subgroup) have been tabulated.

Concomitant medication has been defined as a medication with stop date on or after baseline. If the stop date was unknown the medication is assumed to be "*prior medication*" if the start date is prior to baseline and "*concomitant medication*" if the start date is after baseline.

9.7.1.6 Primary Performance Analysis

9.7.1.6.1 Change from baseline in TVRSS to Week 4

The difference between Active and Placebo in change from baseline up to Week 4 (Visit 3, before second treatment was given) in weekly mean TVRSS has been analysed using an analysis of covariance (ANCOVA) model. The model included treatment and in addition baseline TVRSS as covariate. Least square means (adjusted for the baseline covariates) for each treatment group and the difference in the least square means are presented along with the corresponding 95% confidence interval and p-value.

In addition, descriptive statistics by treatment group is presented. Graphs of weekly mean TVRSS plotted versus week showing the mean in the two treatment groups have been produced. These analyses have been performed also by sex (males, females), type of diagnosis (non-allergic rhinitis, rhinitis medicamentosa, combination) and age (18 - <35, 35 - <50, 50-65).

9.7.1.7 Secondary Performance Analyses

9.7.1.7.1 Change from baseline in TVRSS to Weeks 8, 12 and 24

Change from baseline to Weeks 8, 12 and 24 in weekly mean TVRSS has been analysed in the same way as the primary efficacy/performance endpoint but comparing two active treatments (Active + Active) with one active treatment (Placebo + Active).

9.7.1.7.2 Change from baseline in individual symptom scores (TVRSS)

Change from baseline in weekly median of each individual nasal congestion symptom score (rhinorrhea, postnasal drip and sneezing) has been analysed using a proportional odds model. The model included weekly median baseline value of the symptom score as covariate and tested:

- The difference between Active and Placebo in change from baseline to Week 4 (before second treatment was given) in respective symptom score.
- The difference between two active treatments (Active + Active) and one active treatment (Placebo + Active) in change from baseline to Weeks 8, 12 and 24 in respective symptom score.

The Score test for proportional odds assumption in SAS (Version 9.3) has been used to test the assumption that all logit surfaces were parallel. A non-significant test was taken as evidence that the logit surfaces were parallel and that the odds ratios could be interpreted as constant across all possible cut points of the outcome. None of the tests were significant and thus extended Mantel-Haenszel analyses were not performed.

Counts and percentages of subjects in each category are presented for each of the symptoms by visit. At each post baseline visit, number and percentage of subjects in change categories (IMPROVED, NO CHANGE and WORSENED) are presented. In addition, shift tables of baseline versus each post baseline visit have been produced. The weekly median value has been used for these presentations.

9.7.1.7.3 Change in Peak Nasal Inspiratory Flow (PNIF)

Change from baseline in PNIF has been presented using descriptive statistics by treatment. For descriptive summaries the highest of measurement no. 2 and 3 for each subject has been used.

9.7.1.7.4 Change in rhinosinusitis-specific quality of life (SNOT-22 questionnaire)

Change from baseline in SNOT-22 summary score is presented by descriptive statistics for each visit. Counts and percentages of subjects in each category have been presented for each of the 22 questions separately. The proportion of subjects reporting the symptom as one of the five most significant problems is presented by descriptive statistics for each symptom.

9.7.1.7.5 Change in functional disability and health-related quality of life (EQ-5D-3L questionnaire)

Counts and percentages of subjects in each category (no problems/some or moderate problems/extreme problems) are presented for each of the five dimensions by visit. At each post baseline visit, number and percentage of subjects in change categories (improved, no change and worsened) are presented. Shift tables of baseline versus each post baseline visit have been produced. EQ VAS has been presented using descriptive statistics.

9.7.1.7.6 Use of rescue medication

Descriptive statistics of the cumulative number of days with rescue medication up to Week 4 has been presented.

9.7.1.8 Adverse Events/Adverse Device Effects

AEs have been coded by SOC and PT by qualified staff using MedDRA version 16.0E.

The total number and percentage of subjects with at least one AE/Adverse Device Effect (ADE) and the number of AEs/ADEs have been presented using descriptive statistics. Presentations by SOC and PT have been produced.

AEs have also been tabulated by severity and relationship to treatment.

9.7.2 Determination of Sample Size

This investigation aimed to show a minimal relevant difference in change in TVRSS of 1. The standard deviation of change in TVRSS was assumed to be 2.1 in both the active treatment and the Placebo group (11). To assure 80% power to detect a difference of 1 on the 5% significance level a total sample size of 142 subjects (71 in each group) were needed. To adjust for withdrawals, 158 subjects were to be included in the investigation.

The sample size was re-calculated based on the results from the first interim analysis described in sections 9.7.3 and 9.8.1.3. Based on the same assumptions as the initial sample size calculation above, 79 subjects were needed in the Placebo group (see section 9.8.1.2) and an additional 30 in the active group. Due to that the randomization was to be performed in blocks it was decided to randomize 31 subjects to active treatment and 79 subjects to the Placebo treatment resulting in a total of 80 subjects randomized to active treatment, 79 to Placebo and 48 to Low amplitude control, in total 207 subjects.

9.7.3 Interim Analysis

An interim analysis with the aim to achieve safety and efficacy interim data to be used for strategy and design of future investigations was planned when at least 50% of the subjects had completed Visit 3 or at a predefined cut-off date for the occasion that 50% of the subjects had completed Visit 3 before the cut-off date. At the time of the interim analysis (cut-off date of 2013-06-20), 48 subjects were randomized to Low amplitude control and 49 to active treatment. A total of 91 subjects, 47 in the Active and 44 in the Low amplitude control group had a Visit 2 performed before the cut-off date of 2013-06-20 and were thus included in the analysis. The results from this analysis indicated that the Low amplitude control procedure might have an effect. The Low amplitude control procedure was therefore modified to just insert the balloon into the nostrils without neither inflating the catheter nor stimulating the mucosa by oscillations (called Placebo). The sample size was re-calculated as described in sections 9.7.2 and 9.8.1.3.

A second interim analysis was performed as described in section 9.8.3.

9.8 CHANGES IN THE CONDUCT OF THE INVESTIGATION OR PLANNED ANALYSES

9.8.1 Revised CIP, Version B

A revised CIP (Version B, 2013-07-05) was approved by the Regional Ethics Committee in Stockholm on 2013-07-23. The changes made to the original CIP (Version A, 2013-02-21) have been included and highlighted in the relevant sections of the report, with reference to this section, and are described in detail below.

9.8.1.1 Change of investigation site

In the original version of the CIP (version A) the following clinic was mentioned as Site 004:

Site 004	**Principal Investigator**
Division of Ear, Nose and Throat Diseases Örebro County council Box 1613 SE-70116, Örebro, Sweden	Stig Rudblad, MD, PhD Phone: +46 (0)19 602 1000 E-mail: stig.rudblad@orebroll.se

However, this site was not initiated and was instead replaced by the following site:

Site 004	**Principal Investigator**
Division of Ear, Nose and Throat Diseases Västmanlands Hospital Västerås SE-72189, Västerås, Sweden	Johan Knutsson, MD, PhD Phone: +46 (0)21 173016 E-mail: johan.knutsson@ltv.se

CIP sections affected:

Section 2; Synopsis

Section 5; Clinical Investigators and Clinical Investigation Administrative Structure

9.8.1.2 Modification of the control treatment

The results from the first interim analysis indicated that the Low amplitude control procedure might have an effect. The Low amplitude control procedure was therefore modified to just insert the balloon into the nostrils without neither inflating the catheter nor stimulating the mucosa by oscillations (called Placebo). The treating personnel would not be able to distinguish between active treatment and Placebo.

CIP sections affected:

Section 8.7.2.1; Primary Performance Endpoint

Section 8.7.2.2; Secondary Safety and Performance Endpoints

Section 8.10.1.2; Treatment Comparisons

Section 8.10.1.4; Summary Statistics

Section 8.10.1.6; Secondary Performance Analyses

Section 8.10.3; Determination of Sample Size

Section 8.10.5; Multiplicity

9.8.1.3 Re-calculation of sample size

Based on the same assumptions as the previous sample size calculation, 79 subjects were needed in the Placebo group and an additional 30 in the Active group. Due to that the randomization was to be performed in blocks it was decided to randomize 31 subjects to active treatment and 79 subjects to the Placebo treatment. The total number of subjects randomized was therefore planned to be 207; 80 to active treatment, 79 to Placebo and 48 to Low amplitude control.

A second interim analysis was added. This interim analysis was to be performed when at least 50% of the Placebo subjects had completed Visit 3.

CIP sections affected:

Synopsis

Section 8.4.1; Number of subjects

9.8.2 Additional investigation site

The following additional investigation site was approved by the Regional Ethics Committee in Stockholm on 2013-09-10:

Site 006	**Principal Investigator**
Liby & Rönndahl Primary care clinic Kungsgatan 32 SE-411 19 Göteborg, Sweden	Jan-Eric Friis-Liby, MD Phone: +46 (0)31 76176366 E-mail: janne@liby-ronndahl.se

CIP sections affected:

Section 5; Clinical Investigators and Clinical Investigation Administrative Structure

9.8.3 Changes in the planned statistical analysis

9.8.3.1 A second interim analysis

As described in section 9.8.1.2, the study design was modified as a result of the first interim analysis. Since the option to include a Placebo group and not include additional subjects in the Low amplitude control group was not planned in advance, it was decided to perform a second interim analysis when at least 50% of the Placebo subjects were estimated to have completed Visit 3 (Week 4). The cut-off date for the second interim analysis was set to 2013-12-16 and data from subjects having a weekly mean

TVRSS value at Week 4 on the cut-off date were included in the analysis. The analysis included 65 subjects in the Active group and 41 subjects in the Placebo group.

9.8.3.2 EQ-5D-3L index score not calculated

A joint decision between the Sponsor and the statistician at PCG was taken to not present the EQ-5D-3L index value mentioned in the SAP and in the CIP in this report. The reason for this decision was unavailability of the health economist at Chordate Medical to perform these calculations. The EQ-5D-3L index will therefore be calculated and reported later.

9.8.3.3 Definition of baseline

In the CIP, a baseline measurement was defined as the last non-missing assessment made before treatment start. For PNIF and EQ-5D-3L, a measurement was performed at Visit 2 (Week 0) before first investigational treatment. For these variables, the screening assessment has however been used as baseline to ensure that all baseline measurements were actually performed before treatment.

10 INVESTIGATIONAL SUBJECTS

10.1 Disposition of subjects

The disposition of subjects by treatment group is presented in Table 10.1.

Table 10.1 Disposition of subjects

	Active	Low amplitude control	Placebo	Total
Total number of subjects screened				258
Screen failures				50
Randomized subjects	81	48	79	208
Randomized but not treated		1		1[1]
-Subjects receiving treatment 1	81	47	79	207
-Subjects receiving treatment 2	199	-	-	199
Completed subjects	77	40	75	192
Withdrawn subjects	4	7	4	15

[1]Subject SE0318 was a screening failure but was by mistake randomized, however in the analyses not included among Randomized subjects.

A total of 258 subjects were screened for participation in the study. Fifty (50) of the subjects screened were not eligible for randomisation and were classified as screen failures. Note that one subject (SE0318) was randomized by mistake and was therefore not treated or included among subjects randomized. The reasons for screen failure are listed in Table 10.2.

Table 10.2 Screen failures

	Reason for screen failure	No of subjects
Inclusion criterion not fulfilled		**13***
1	Persistent (>12w) symptoms of idiopathic rhinitis dominated by nasal congestion (± secretion) for an average of at least 1 h per day for at least 5 days during a period of 14 days	3
2	Having nasal congestion as major symptom, and a nasal congestion score of at least 2 (scale 0-3)	6
4	Suitable for participation in the study without safety concerns based on medical history and physical examination	5
6	Willing and able to comply with all study related procedures	1
Exclusion criterion fulfilled		**41***
1	Allergic rhinitis, demonstrated by either positive skin prick test, phadiatop or RAST	26
6	Pronounced anterior septal deviation or other significant nasal pathology at endoscopic examination	14
9	Any disease, condition (medical or surgical) which, in the opinion of the investigator, might compromise the study results, or would place the subject at increased risk	4
Total no. of screening failures		**50**

*Note that some subjects have more than one criterion fulfilled/not fulfilled

Of the 207 subjects correctly randomized, 81 were allocated to active treatment at the first treatment visit. All subjects in the active treatment group have been used in the main analyses. However, in some presentations subjects randomized before the first interim analysis (49; called “Old” Active) and after (32; called “New” Active) have been presented separately. Forty-seven (47) subjects received Low amplitude control up to the first interim analysis and 79 subjects were treated with Placebo.

A total of 15 subjects were withdrawn from study participation for the reasons listed in Table 10.3.

Table 10.3 Premature termination

	Standardized Disposition Term	Active	Low amplitude control	Placebo	Total
Not completed		4 (4.9%)	7 (14.9%)	4 (5.1%)	15 (7.2%)
Reason for withdrawal	Subject's request	1	3	2	6
	Adverse Event	0	2	0	2
	Investigator/Sponsor's decision	0	0	1	1
	Lost to Follow-up	3	2	0	5
	Other	0	0	1	1

Eight subjects were withdrawn before receiving the second treatment at Visit 3 and seven subjects did not complete the follow-up period. Two subjects in the Low amplitude control group were withdrawn due to AEs (see section 12.2). Subjects discontinued are listed in Appendix 16.2.1.

The number and percentage of subjects recruited by month is displayed by treatment group in Table 10.4.

Table 10.4 Month of recruitment

Month of Informed consent	Active N=81	Low amplitude control N=47	Placebo N=79	Total N=207
April	30 (37.0%)	30 (63.8%)	0	60 (29.0%)
May	18 (22.2%)	17 (36.2%)	0	35 (16.9%)
June	1 (1.2%)	0	0	1 (0.5%)
July	0	0	0	0
August	0	0	0	0
September	8 (9.9%)	0	13 (16.5%)	21 (10.1%)
October	2 (2.5%)	0	6 (7.6%)	8 (3.9%)
November	9 (11.1%)	0	25 (31.6%)	34 (16.4%)
December	6 (7.4%)	0	19 (24.1%)	25 (12.1%)
January	4 (4.9%)	0	12 (15.2%)	16 (7.7%)
February	3 (3.7%)	0	4 (5.1%)	7 (3.4%)
March	0	0	0	0

All subjects included in the Low amplitude control group and 59.2% of the total Active group were recruited during April and May. All subjects in the Placebo group (used for the main analyses) were recruited during September – February with 55.7% being treated during November and December. No subjects were enrolled during March, July and August.

The number of subjects recruited at each participating site is presented in Table 14.1 (section 14).

10.2 CIP deviations

A major CIP violation was defined as a deviation from the CIP procedures affecting the assessment of efficacy/performance (e.g termination of participation in the investigation before the primary endpoint follow-up (Week 4) or deviation from the inclusion/exclusion criteria.

CIP deviations were classified as major violations or minor deviations by the Sponsor, Project Manager and Statistician at the clean file meeting, prior to database closure and code breaking. A major CIP violation excluded the subject from the PPAS. All major CIP violations are listed by subject in Table 10.5.

Table 10.5 Major CIP violations

Deviation	Subjects
Treatment not given according to CIP	SE406*, SE410
Nasal Congestion Symptom score median was not ≥ 2 (inclusion criterion no. 2 not fulfilled)	SE0103, SE0113, SE0202, SE0203, SE0206, SE0213, SE0235, SE0250, SE0251, SE0260, SE0271, SE0275, SE0285, SE0289, SE0309, SE0313, SE0326, SE0406*, SE0412, SE0416, SE0419, SE0420, SE0512, SE0514*, SE0516, SE0518, SE0519, SE0612, SE0613, SE0618, SE0626, SE0647
No Week 4 assessments available	SE107, SE0128, SE0139, SE0317, SE0514*

*Note that two major violations were reported for subjects SE0406 and SE0514

Thirty-seven (37) subjects randomized were excluded from the PPAS due to major CIP deviations.

CIP deviations not fulfilling the criteria for major violation were classified as minor. All CIP deviations are listed by subject in Appendix 16.2.2.

11 EFFICACY/PERFORMANCE EVALUATION

11.1 Data sets analysed

Prior to closure of the database all subjects randomized were classified and included in the different analysis populations defined in section 9.7.1.2. The number of subjects in each data set is presented in Table 11.1.

Table 11.1 Data sets analysed

	Active	Low amplitude control	Placebo	Total
Full analysis set (FAS)	81	47	79	207
Per protocol analysis set (PPAS)	67	40	63	170
Safety analysis set	81	47	79	207

The FAS has been used for all primary and secondary efficacy performance analyses. The PPAS has been used for the efficacy/performance analysis of TVRSS (primary and secondary) to investigate the sensitivity of the results from the FAS analysis.

A total of 207 subjects were included in the FAS and safety populations, whereof 81 subjects received active treatment at the first treatment visit and 126 subjects were included in the control group. The control procedure used before the first interim analysis is called Low amplitude control and was used for 47 subjects whereas the control procedure used following the first interim analysis is called Placebo and was used for 79 subjects. In the efficacy/performance analyses the main comparisons have been made between active treatment and Placebo only (81+79=160 subjects in FAS). In tables with descriptive statistics presented also for the Low amplitude control, the Active group has been divided into subjects treated before and after the first interim analysis ("Old" and "New" Active, respectively).

Thirty-seven (37) subjects were excluded from the PPAS due to major protocol violations (see section 10.2). Subjects excluded from the analyses are listed in Appendix 16.2.3.

11.2 Demographics and other baseline characteristics

11.2.1 Demographics

Demographic information recorded in the e-CRF at baseline included age (year), gender, weight (kg) and height (cm). Descriptive statistics for these variables are presented by treatment for the FAS in Table 11.2.

Table 11.2 Demographics, FAS

		Active N=81	Low amplitude control N=47	Placebo N=79	Total N=207
Age (years)	n/nmiss	81/0	47/0	79/0	207/0
	Mean (SD)	46.4 (12.0)	49.0 (10.0)	45.6 (13.6)	46.7 (12.2)
	Median (Min, Max)	47.0 (18, 65)	50.0 (25, 65)	49.0 (18, 65)	49.0 (18, 65)
Gender	Male	36 (44.4%)	34 (72.3%)	43 (54.4%)	113 (54.6%)
	Female	45 (55.6%)	13 (27.7%)	36 (45.6%)	94 (45.4%)
Weight (kg)	n/nmiss	81/0	47/0	79/0	207/0
	Mean (SD)	77.2 (16.0)	80.7 (16.2)	77.9 (15.3)	78.3 (15.8)
	Median (Min, Max)	77.0 (50, 115)	79.0 (50, 114)	79.0 (51, 115)	77.0 (50, 115)
Height (cm)	n/nmiss	81/0	47/0	79/0	207/0
	Mean (SD)	173.5 (9.9)	176.7 (8.1)	174.9 (9.5)	174.8 (9.4)
	Median (Min, Max)	173.0 (151, 198)	178.0 (156, 193)	175.0 (155, 195)	175.0 (151, 198)

Max= Maximum, Min = Minimum, nmiss = number of missing values, SD = Standard deviation

Percentages are based on the number of subjects within each treatment group. Weight and height measured at Visit 1.

The mean age, weight and height were similar across the treatment groups. The mean age ± SD among all subjects randomized was 46.7 ± 12.2 years (median 49.0). The majority of the subjects in the Low amplitude control group (72.3%) were males while both genders were more equally represented in the other two treatment groups.

Demographics presented by subjects treated before the first interim analysis ("Old" Active and Low amplitude control) and after ("New" Active and Placebo) separately, are included in section 14.2 (Table 14.2).

Individual subject data for demographics are listed in Appendix 16.2.4.1.

11.2.2 Medical history and concurrent diseases

Any clinically relevant medical or surgical history and/or any concomitant diseases ongoing at study initiation were recorded at Visit 1 (screening). Medical history is presented by MedDRA SOC and PT in Table 11.3.

Table 11.3 Medical history, Safety analysis set

System Organ Class/Preferred Term*	Active N=81		Placebo N=79	
	n (%)	m	n (%)	m
Any medical history	13 (16.0%)	15	14 (17.7%)	20
Injury, poisoning and procedural complications	**4 (4.9%)**	**4**	**9 (11.4%)**	**9**
Face injury	3 (3.7%)	3	7 (8.9%)	7
Joint injury	1 (1.2%)	1	0	0
Facial bones fracture	0	0	1 (1.3%)	1
Injury	0	0	1 (1.3%)	1
Surgical and medical procedures	**4 (4.9%)**	**5**	**2 (2.5%)**	**4**
Cataract operation	0	0	1 (1.3%)	2
Adenoidectomy	1 (1.2%)	1	0	0
Elbow operation	1 (1.2%)	1	0	0
Foot operation	1 (1.2%)	1	0	0
Jaw operation	1 (1.2%)	1	0	0
Tonsillectomy	1 (1.2%)	1	0	0
Genitourinary operation	0	0	1 (1.3%)	1
Tooth extraction	0	0	1 (1.3%)	1
Infections and infestations	**3 (3.7%)**	**3**	**2 (2.5%)**	**2**
Nasopharyngitis	2 (2.5%)	2	2 (2.5%)	2
Gastroenteritis	1 (1.2%)	1	0	0
Nervous system disorders	**2 (2.5%)**	**2**	**2 (2.5%)**	**3**
Headache	1 (1.2%)	1	2 (2.5%)	3
Migraine	1 (1.2%)	1	0	0
Cardiac disorders	**1 (1.2%)**	**1**	**0**	**0**
Myocardial infarction	1 (1.2%)	1	0	0
Gastrointestinal disorders	0	0	1 (1.3%)	1
Toothache	0	0	1 (1.3%)	1
Respiratory, thoracic and mediastinal disorders	0	0	1 (1.3%)	1
Oropharyngeal pain	0	0	1 (1.3%)	1

n = number of patients, m = number of mentions, *Coded acc to MedDRA version 16.0E
Percentages are based on the number of subjects within each treatment group
Partially missing start and stop date were manually classified as medical history or concurrent disease

The two treatment groups were similar as regards medical history reported. Any medical history was reported by 13 (16.0%) of the subjects receiving active treatment at the first treatment visit and by 14 (17.7%) of the subjects treated with the Placebo procedure. Three (3) subjects (3.7%) of in the Active group and 7 subjects (8.9%) treated with Placebo had a history of facial injury.

A summary of concurrent diseases, ongoing at study start, are presented by MedDRA SOC in Table 11.4. A more detailed listing, including PT, is available in section 14.2 (Table 14.3).

Table 11.4 Summary of concurrent diseases, Safety analysis set

System Organ Class	Active N=81		Placebo N=79	
	n (%)	m	n (%)	m
Any medical history	62 (76.5%)	113	67 (84.8%)	125
Respiratory, thoracic and mediastinal disorders	50 (61.7%)	59	57 (72.2%)	64
Endocrine disorders	5 (6.2%)	5	10 (12.7%)	10
Vascular disorders	**6 (7.4%)**	**6**	**10 (12.7%)**	**10**
Nervous system disorders	8 (9.9%)	9	5 (6.3%)	6
Psychiatric disorders	6 (7.4%)	7	5 (6.3%)	5
Gastrointestinal disorders	4 (4.9%)	6	6 (7.6%)	6
Musculoskeletal and connective tissue disorders	4 (4.9%)	4	6 (7.6%)	6
Metabolism and nutrition disorders	5 (6.2%)	5	1 (1.3%)	1
Reproductive system and breast disorders	1 (1.2%)	1	4 (5.1%)	4
Skin and subcutaneous tissue disorders	0	0	4 (5.1%)	4
Infections and infestations	3 (3.7%)	3	2 (2.5%)	2
Congenital, familial and genetic disorders	0	0	2 (2.5%)	2
Cardiac disorders	1 (1.2%)	1	1 (1.3%)	1
Ear and labyrinth disorders	1 (1.2%)	1	0	0
Eye disorders	1 (1.2%)	1	1 (1.3%)	1
Immune system disorders	1 (1.2%)	1	0	0
Injury, poisoning and procedural complications	1 (1.2%)	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.2%)	1	0	0
Social circumstances	1 (1.2%)	1	0	0
Surgical and medical procedures	1 (1.2%)	1	0	0
General disorders and administration site conditions	0	0	1 (1.3%)	1
Investigations	0	0	1 (1.3%)	1
Renal and urinary disorders	0	0	1 (1.3%)	1

n = number of patients, m = number of mentions

Percentages are based on the number of subjects within each treatment group

Partially missing start and stop date were manually classified as medical history or concurrent disease

Any concurrent disease was reported by 62 subjects (76.5%) in the Active group and by 67 subjects (84.8%) treated with Placebo at the first treatment visit. The majority of the diseases in both treatment groups were within the SOC *Respiratory, thoracic and mediastinal disorders*. *Nasal inflammation* occurred in 32.1% of subjects in the Active group and in 26.6% of the Placebo subjects. Corresponding figures for N*asal turbinate hypertrophy* and N*asal congestion* were 13.6/25.3% and 11.1/20.3%, respectively.

Individual subject data for medical history are listed in Appendix 16.2.4.2.

11.2.3 Prior and concomitant medications

Medications used were recorded in the e-CRF at screening and the records were updated throughout the investigation. Medications stopped before baseline (before first treatment at Visit 2) have been defined as prior medications and medications stopped on or after baseline have been defined as concomitant medications. If the stop date is unknown the medication is assumed to be prior if the start date is prior to baseline and concomitant if the start date is after baseline.

Prior medications are presented in Table 14.4 and concomitant medications in Table 14.5 (section 14.2). Therapeutic main groups (ATC level 2) are presented in descending order of frequency and chemical substance subgroups (ATC level 5) in the same order within each therapeutic main group.

The use of prior medications was similar in the two treatment groups. In the Active group, 9 subjects (11.1%) reported intake of a total of 10 medications prior to start of treatment compared to 10 subjects (12.7%) reporting a total of 16 medications in the Placebo group. The most commonly reported therapeutic main groups were A*nalgesics* and *Nasal preparations,* in both treatment groups.

Among the subjects receiving active treatment at the first treatment visit, 56 (69.1%) reported intake of any concomitant medication during the study as compared to 67 subjects (84.8%) treated with Placebo. The most commonly reported therapeutic main groups were *Nasal preparations, Analgesics* and *Anti-inflammatory and antirheumatic products,* in both treatment groups. The nasal preparations most frequently used were mometasone (used by 21.0% in the Active group and by 24.1% of the Placebo subjects), oxymetazoline (used by 17.3% in the Active group and by 22.8% of the Placebo subjects) and xylometazoline (used by 12.3% in the Active group and by 17.7% of the Placebo subjects). Paracetamol was the analgesic most commonly reported (used by 21.0% in the Active group and by 21.5% of the Placebo subjects).

Individual subject data for Prior and concomitant medications are listed in Appendix 16.2.4.3.

11.3 Measurements of treatment compliance

Treatment with the device was administered by trained personnel in compliance with the CIP and the manufacturer's instructions for use. The device was supplied to the Principal Investigator with pre-set algorithms defined for the clinical investigation. Two major deviations from the prescribed technique and timing were recorded:

SE0406: Treatment was not given according to CIP (long break between sides).

SE0410: Treatment 1 was not given according to CIP (too short total treatment time).

11.4 Analysis of Primary efficacy/performance endpoint

11.4.1 Change in TVRSS from baseline to Week 4

The primary endpoint was change in weekly mean TVRSS from baseline to Week 4 (Visit 3, before second treatment was given). Summary statistics are presented for the FAS population in Table 11.5 and for the PPAS population in Table 14.6 (section 14.3.1).

Table 11.5 Summary of weekly mean TVRSS and change from baseline up to Week 4, FAS

Week	Statistic	Active N=81	Placebo N=79
Week -1	n	81	79
	Mean (SD)	4.04 (1.64)	3.80 (1.40)
	95% CI	(3.67, 4.40)	(3.49, 4.11)
	Median	4.00	3.43
	Q1, Q3	2.67, 5.00	2.50, 4.75
	Min, Max	1.2, 8.7	1.5, 7.7
Week 1	n	81	79
	Mean (SD)	3.62 (1.71)	3.79 (1.68)
	95% CI	(3.24, 4.00)	(3.41, 4.16)
	Median	3.43	3.50
	Q1, Q3	2.33, 4.57	2.67, 4.71
	Min, Max	0.9, 9.3	1.3, 9.0
Week 2	n	81	79
	Mean (SD)	3.41 (1.81)	3.77 (1.78)
	95% CI	(3.01, 3.81)	(3.37, 4.17)
	Median	3.14	3.50
	Q1, Q3	2.00, 4.33	2.33, 4.71
	Min, Max	0.5, 10.0	0.4, 9.6
Change from baseline, Week 2	n	81	79
	Mean (SD)	-0.63 (1.53)	-0.03 (1.35)
	95% CI	(-0.97, -0.29)	(-0.33, 0.27)
	Median	-0.43	-0.07
	Q1, Q3	-1.38, 0.19	-0.79, 0.55
	Min, Max	-4.5, 4.0	-3.6, 4.5
Week 3	n	80	79
	Mean (SD)	3.44 (1.80)	3.65 (1.81)
	95% CI	(3.04, 3.84)	(3.24, 4.06)
	Median	3.23	3.20
	Q1, Q3	2.07, 4.61	2.57, 4.71
	Min, Max	0.3, 9.0	0.9, 8.8

Table 11.5 Summary of weekly mean TVRSS and change from baseline up to Week 4, FAS *(-continued)*

Week	Statistic	Active N=81	Placebo N=79
Change from baseline, Week 3	N	80	79
	Mean (SD)	-0.56 (1.67)	-0.15 (1.58)
	95% CI	(-0.93, -0.19)	(-0.50, 0.20)
	Median	-0.56	-0.36
	Q1, Q3	-1.51, 0.50	-1.25, 0.57
	Min, Max	-5.1, 5.0	-3.9, 4.6
Week 4	n	78	79
	Mean (SD)	3.34 (1.58)	3.61 (1.82)
	95% CI	(2.98, 3.70)	(3.20, 4.02)
	Median	3.17	3.43
	Q1, Q3	2.29, 4.29	2.33, 4.67
	Min, Max	0.1, 8.6	0.5, 10.8
Change from baseline, Week 4	n	78	79
	Mean (SD)	-0.68 (1.42)	-0.19 (1.44)
	95% CI	(-1.00, -0.36)	(-0.51, 0.13)
	Median	-0.58	-0.29
	Q1, Q3	-1.54, 0.14	-1.10, 0.50
	Min, Max	-4.7, 2.5	-3.9, 4.1

The difference between active treatment and Placebo in change from baseline to Week 4 has been analysed using an analysis of covariance (ANCOVA) model for the FAS population (Table 11.6) and for the PPAS population (Table 11.7). The model included treatment and baseline mean TVRSS as covariate. Least square means (LS mean) (adjusted for the baseline value) for each treatment group and the difference in the LS means are presented along with the corresponding 95% confidence interval and p-value.

Table 11.6 ANCOVA analysis of change from baseline in weekly mean TVRSS at Week 4, FAS

		Estimate		Difference to Placebo		
Treatment	n	LS mean	95% CI	LS mean	95% CI	P-value
Active	78	-0.645	-0.947, -0.342	-0.421	-0.848, 0.006	0.0531
Placebo	79	-0.223	-0.524, 0.077			

Table 11.7 ANCOVA analysis of change from baseline in weekly mean TVRSS at Week 4, PPAS

		Estimate		Difference to Placebo		
Treatment	n	LS mean	95% CI	LS mean	95% CI	P-value
Active	67	-0.775	-1.105, -0.445	-0.512	-0.986, -0.037	0.0349
Placebo	63	-0.263	-0.603, 0.077			

In the FAS population, the weekly mean TVRSS decreased significantly more from baseline to Week 4 in the Active group as compared to Placebo (p=0.0531). The difference between treatments in LS mean change was -0.421 (CI: -0.848 to 0.006). The significant result for the FAS was supported by the difference detected for the PPAS population (p=0.0349).

The weekly mean TVRSS by treatment up to Week 4 is displayed for the FAS population in Figure 11.1 and for the PPAS population in Figure 11.2. TVRSS mean by treatment and day up to Week 4 are presented for the FAS and PPAS populations in Figure 14.1 and Figure 14.2 (section 14.3.1).

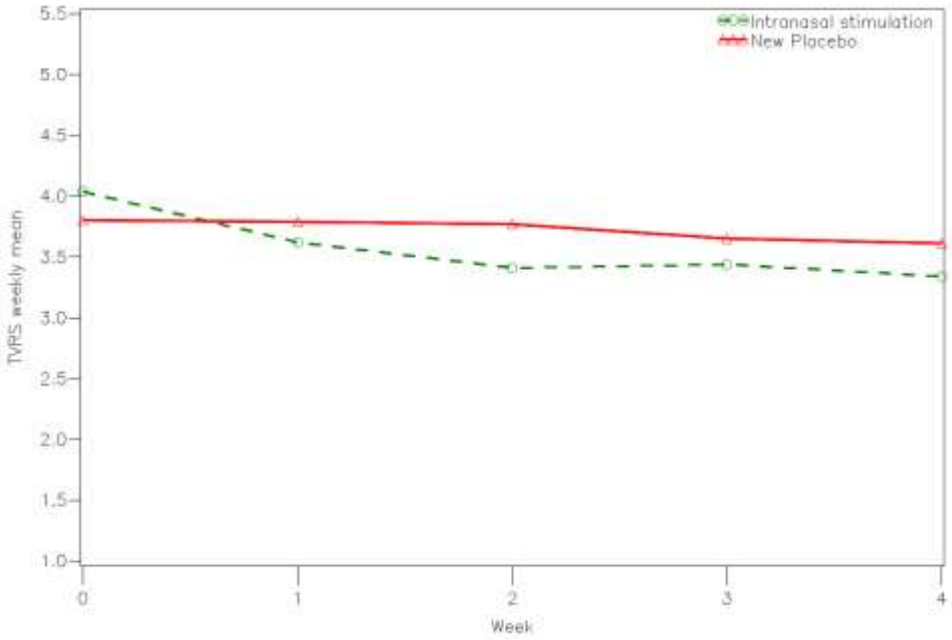


Figure 11.1 Weekly mean TVRSS by treatment up to Week 4, FAS

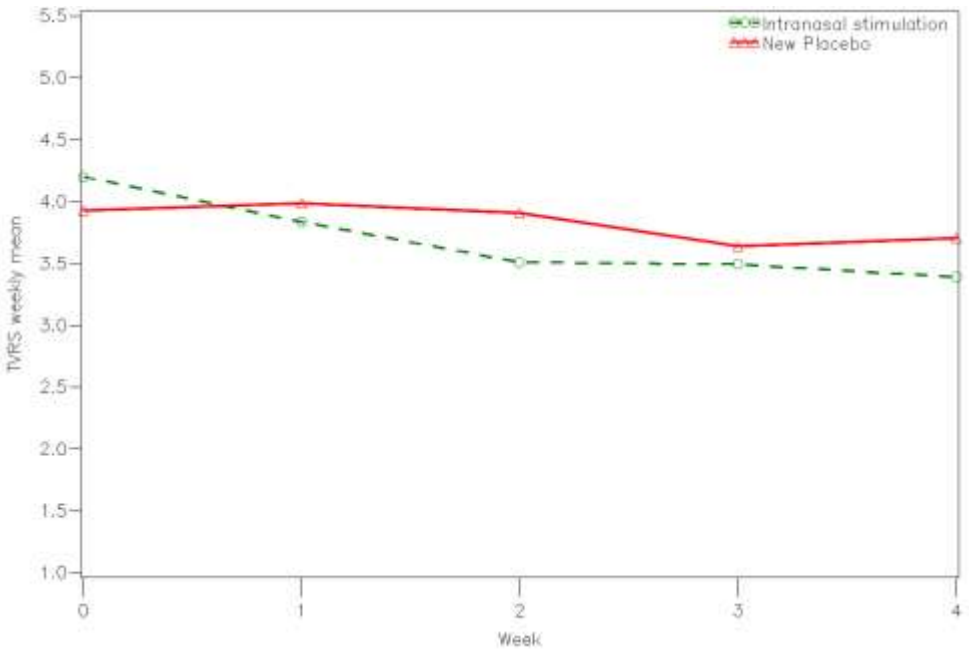


Figure 11.2 Weekly mean TVRSS by treatment up to Week 4, PPAS

Summary statistics for change in weekly mean TVRSS from baseline up to Week 4, presenting subjects treated before the first interim analysis ("Old" Active and Low amplitude control) and after ("New" Active and Placebo) separately, are included in Table 14.7 (FAS) and Table 14.8 (PPAS), in section 14.3.1.

11.4.2 Change in TVRSS from baseline to Week 4, sub-group analyses

The same analyses as presented in section 11.4.1 have also been performed for the following sub-groups: gender (males, females), type of diagnosis (non-allergic rhinitis, rhinitis medicamentosa, combination) and age (18 - <35, 35 - <50, 50-65). Summary statistics and analysis of the difference between active treatment and Placebo are presented for the FAS population in Table 14.9 - Table 14.18 (section 14.3.1).

<u>Gender</u>

The weekly mean TVRSS at baseline was similar between males and females and across treatment groups. For both genders, the mean TVRSS decreased more over time up to Week 4 in the Active group as compared to Placebo (Table 14.9, Table 14.11). The difference between treatment groups in LS mean change from baseline to Week 4 was statistically significant for females (LS mean difference -0.710 [CI: -1.411 to -0.009], p=0.0471) (Table 14.12). The weekly mean TVRSS by treatment up to Week 4 is displayed for females in Figure 11.3.

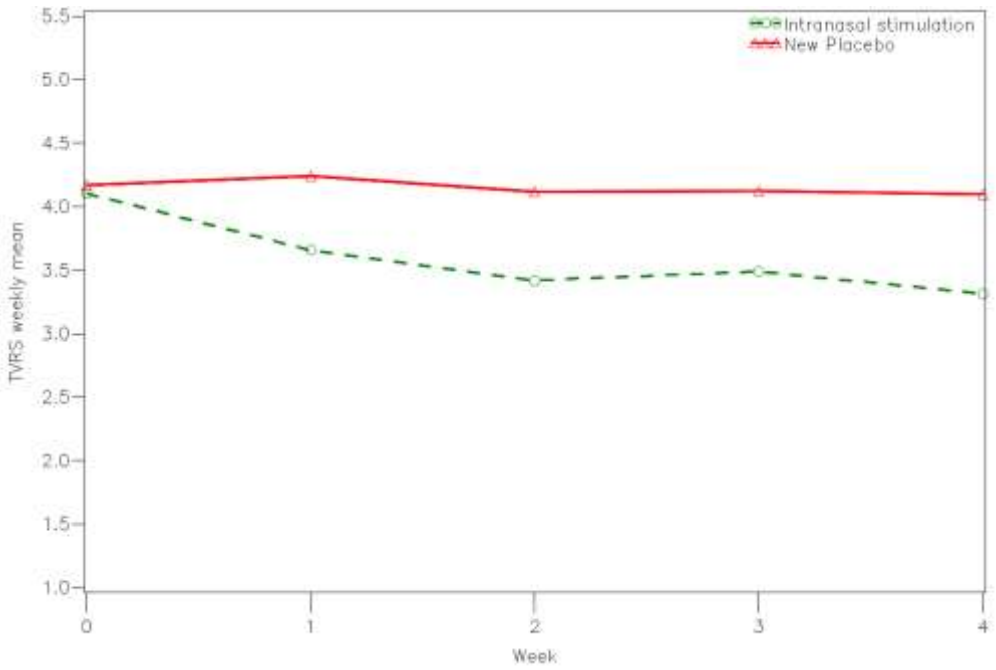


Figure 11.3 Weekly mean TVRSS by treatment up to Week 4, Females, FAS

Type of diagnosis

The weekly mean TVRSS at baseline was similar between treatment groups for subjects with non-allergic rhinitis and rhinitis medicamentosa (Table 14.13, Table 14.15). For subjects with the combination diagnosis the baseline mean TVRSS was higher in the Active group; 5.13 ± 0.87 (median 5.00) as compared to 3.52 ± 1.99 (median 3.00) among subjects treated with Placebo (Table 14.17). It should be noted however that data was available only for a limited number of subjects with the combination diagnosis (7 Active and 3 Placebo).

A statistically significant difference between active treatment and Placebo in change from baseline to Week 4 was detected for subjects with non-allergic rhinitis (p=0.0213). The TVRSS score decreased more after active treatment as compared to Placebo (LS mean difference -0.561 (CI: -1.038 to -0.085) (Table 14.14). The weekly mean TVRSS by treatment up to Week 4 is displayed for the sub-group with non-allergic rhinitis in Figure 11.4.

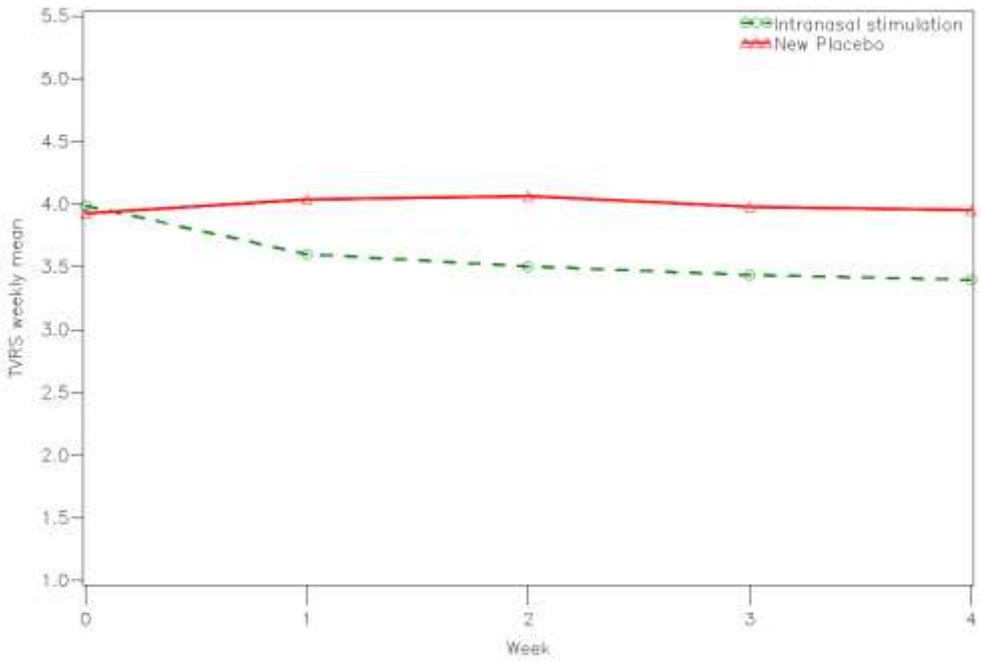


Figure 11.4 Weekly mean TVRSS by treatment up to Week 4, patients with non-allergic rhinitis, FAS

Age groups

The weekly mean TVRSS at baseline was similar between age groups and across treatment groups (Table 14.19, Table 14.21, Table 14.23). A statistically significant better improvement in TVRSS score from baseline to Week 4 after active treatment, as compared to Placebo was detected for subjects in the age group 50-65 years (p=0.0515); the difference between treatments in LS mean change was -0.625 (CI:-1.254 to 0.004) (Table 14.24). The weekly mean TVRSS by treatment up to Week 4 is displayed for the sub-group 50 years or older in Figure 11.5.

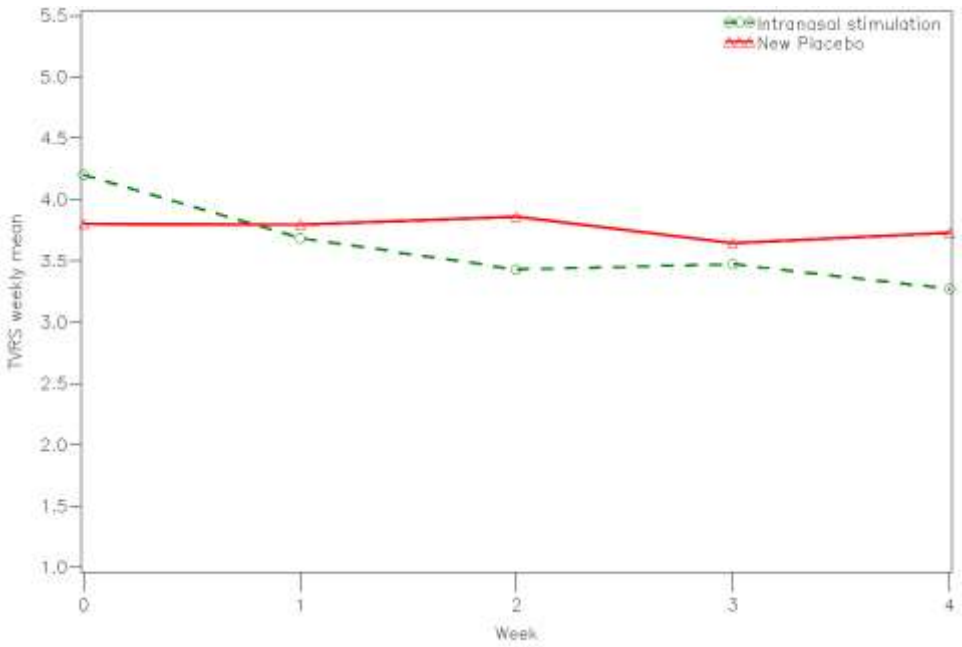


Figure 11.5 Weekly mean TVRSS by treatment up to Week 4, Age group 50-65, FAS

11.5 Analysis of secondary efficacy/performance endpoints

11.5.1 Change in TVRSS from baseline to Weeks 8, 12 and 24

Summary statistics for weekly mean TVRSS and change from baseline to Weeks 5, 6, 7, 8, 12 and 24 are presented for the FAS population in Table 14.25 and for the PPAS population in Table 14.26 (section 14.3.2).

The changes in weekly mean TVRSS from baseline to Weeks 8, 12 and 24 have been compared between subjects receiving two active treatments and subjects given Placebo at the first treatment visit followed by an active treatment at Week 4 using an analysis of covariance (ANCOVA) model for the FAS population (Table 11.8) and for the PPAS population (Table 14.27).

Table 11.8 ANCOVA analysis of weekly mean TVRS at Weeks 8, 12 and 24, FAS

			Estimate		Difference to one active treatment		
Visit	**Treatment**	**n**	**LS mean**	**95% CI**	**LS mean**	**95% CI**	**P-value**
Week 8	Active + Active	73	-1.270	-1.616, -0.923	-0.635	-1.122, -0.148	0.0109
	Placebo + Active	75	-0.634	-0.976, -0.293			
Week 12	Active + Active	77	-1.096	-1.466, -0.727	-0.481	-1.011, 0.049	0.0749
	Placebo + Active	73	-0.615	-0.995, -0.236			
Week 24	Active + Active	70	-0.737	-1.128, -0.347	0.396	-0.162, 0.954	0.1631
	Placebo + Active	68	-1.133	-1.529, -0.737			

The weekly mean TVRSS decreased more in the Two Active group from baseline to Weeks 8 and 12, as compared to One Active. The difference between treatment groups in LS mean change was statistically significant in the FAS population at Week 8 (LS mean difference -0.635 [CI: -1.122 to -0.148], p=0.0109). Similar results were obtained for the PPAS population with a statistically significant difference between treatment groups at Week 8 (p=0.0190) (Table 14.27).

The weekly mean TVRSS by treatment from Week 4 to Week 24 is displayed for the FAS population in Figure 11.6 and for the PPAS population in Figure 14.3.

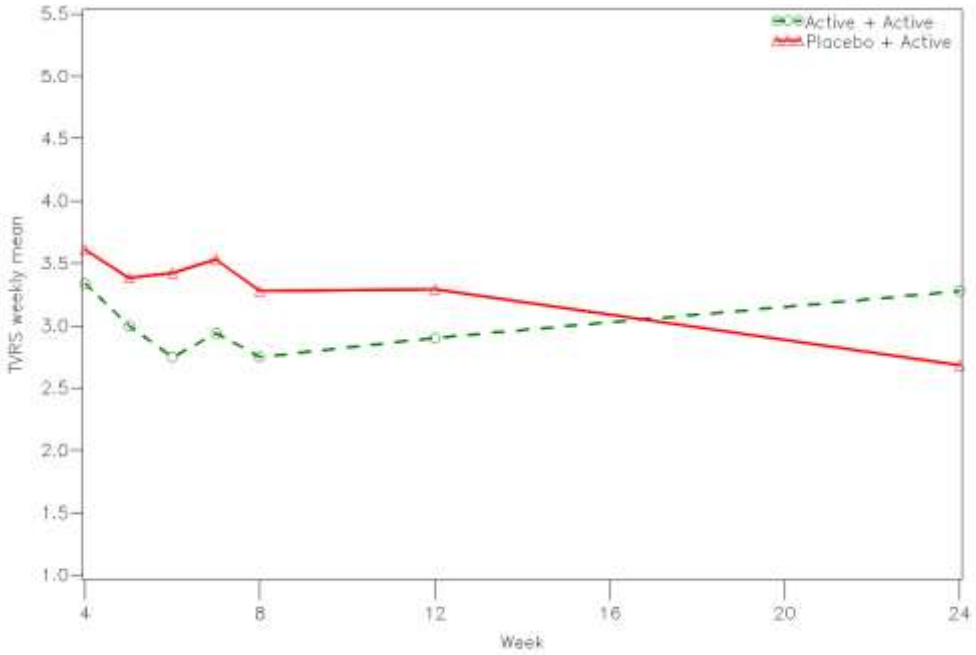


Figure 11.6 Weekly mean TVRSS by treatment from Week 4 to 24, FAS

Summary statistics for weekly mean TVRSS and change from baseline to Weeks 5, 6, 7, 8, 12 and 24, presenting subjects treated before the first interim analysis ("Old" Active and Low amplitude control) and after ("New" Active and Placebo) separately, are included in Table 14.28 (FAS) and Table 14.29 (PPAS), in section 14.3.2.

11.5.2 Change from baseline to Week 4 in individual symptom scores

Summary statistics for weekly median for each of the four individual symptom scores (nasal congestion, rhinorrhea, postnasal drip and sneezing) by week from baseline up to Week 4 and by treatment (*Active/Placebo*) are presented in section 14.3.2 (Table 14.30). A shift table with number and percentage of subjects with the different scores (0=NONE, 1=MILD, 2=MODERATE and 3=SEVERE) at baseline versus Week 4 is included in section 14.3.2 (Table 14.31).

Number and percentage of subjects in the shift categories IMPROVED, NO CHANGE and WORSENED at Week 4, based on weekly median values, are presented in Table 11.9.

Table 11.9 Change from baseline of Weekly median individual symptom score at Week 4, FAS

Parameter	Week	Shift from baseline	Active N=81		Placebo N=79	
			n (%)	95% CI*	n (%)	95% CI*
Nasal Congestion Symptom Score median	Week 4	Improved	33 (42.3%)	(31.2%, 54.0%)	17 (21.5%)	(13.1%, 32.2%)
		No change	40 (51.3%)	(39.7%, 62.8%)	54 (68.4%)	(56.9%, 78.4%)
		Worsened	5 (6.4%)	(2.1%, 14.3%)	8 (10.1%)	(4.5%, 19.0%)
Postnasal Drip Symptom Score median	Week 4	Improved	13 (16.7%)	(9.2%, 26.8%)	15 (19.0%)	(11.0%, 29.4%)
		No change	54 (69.2%)	(57.8%, 79.2%)	50 (63.3%)	(51.7%, 73.9%)
		Worsened	11 (14.1%)	(7.3%, 23.8%)	14 (17.7%)	(10.0%, 27.9%)
Rhinorrhea Symptom Score median	Week 4	Improved	20 (25.6%)	(16.4%, 36.8%)	17 (21.5%)	(13.1%, 32.2%)
		No change	51 (65.4%)	(53.8%, 75.8%)	49 (62.0%)	(50.4%, 72.7%)
		Worsened	7 (9.0%)	(3.7%, 17.6%)	13 (16.5%)	(9.1%, 26.5%)
Sneezing Symptom Score median	Week 4	Improved	11 (14.1%)	(7.3%, 23.8%)	9 (11.4%)	(5.3%, 20.5%)
		No change	58 (74.4%)	(63.2%, 83.6%)	55 (69.6%)	(58.2%, 79.5%)
		Worsened	9 (11.5%)	(5.4%, 20.8%)	15 (19.0%)	(11.0%, 29.4%)

* Confidence intervals calculated using Clopper-Pearson method.

The difference between Active and Placebo in change from baseline to Week 4 has been analysed using a proportional odds model as described in section 9.7.1.7.2. The results from the analyses are presented in Table 11.10. An odds ratio above 1 indicates that active treatment is better than Placebo.

Table 11.10 Proportional odds analysis of individual symptom scores at Week 4, FAS

Parameter	Odds ratio *	95% CI	p-value
Nasal Congestion Symptom Score median	2.49	1.29, 4.82	0.0056
Postnasal Drip Symptom Score median	0.89	0.44, 1.80	0.7352
Rhinorrhea Symptom Score median	1.55	0.76, 3.19	0.2263
Sneezing Symptom Score median	1.23	0.59, 2.59	0.5803

* Odds ratio between Intranasal stimulation and Placebo (ratio of the odds of being in the lower categories) from a proportional odds model controlling for baseline.

A significantly better improvement (more subjects shifting to a lower score) after active treatment as compared to Placebo was seen at Week 4 for the nasal congestion symptom score (odds ratio 2.49 [CI: 1.29 to 4.82], p=0.0056). At this time-point, 33 subjects (42.3%) in the Active group had improved the nasal congestion symptom score as compared to 17 subjects (21.5%) treated with Placebo. Five (5) subjects (6.4%) in the Active group reported worsening of *nasal congestion* as compared to 8 (10.1%) of the Placebo subjects (Table 11.9). A graphic presentation of the median change from baseline to Week 4 is given by treatment in Figure 11.7.

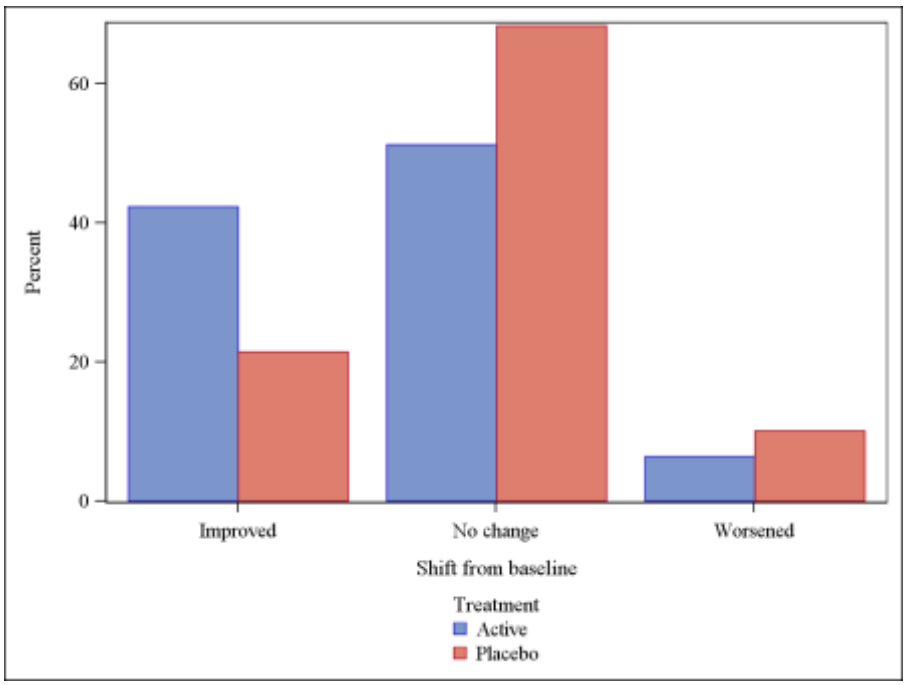


Figure 11.7 Nasal Congestion Symptom Score median change from baseline to Week 4

A better effect of active treatment as compared to Placebo on rhinorrhea and sneezing was indicated by the odds ratio (1.55 [CI: 0.76 to 3.19] and 1.23 [CI: 0.59 to 2.59], respectively). More subjects reported worsening in the Placebo group (16.5% and 19.0%) as compared to the Active group (9.0% and 11.5%), (Table 11.9). For postnasal drip, more subjects seemed to improve after Placebo treatment (odds ratio 0.89 [CI: 0.44 to 1.80]). However, no statistically significant differences were detected for these symptom scores. Graphic presentations of the median change from baseline to Week 4 are given by treatment for each symptom score in section 14.3.2 (Figure 14.4, Figure 14.5 and Figure 14.6).

Summary statistics for weekly median symptom scores at Week 4 and a shift category table (IMPROVED, NO CHANGE and WORSENED), presenting subjects treated before the first interim analysis ("Old" Active and Low amplitude control) and after ("New" Active and Placebo) separately, are included in section 14.3.2 (Table 14.32 and Table 14.33).

11.5.3 Change from baseline to Weeks 8, 12 and 24 in individual symptom scores

Summary statistics for weekly median for each of the four individual symptom scores at Weeks 8, 12 and 24 are presented by treatment group (Two Active/One Active) in Table 14.34 (section 14.3.2). A shift table with number and percentage of subjects with the different scores (0=NONE, 1=MILD, 2=MODERATE and 3=SEVERE) at baseline versus Weeks 8, 12 and 24 is included in section 14.3.2 (Table 14.35).

Number and percentage of subjects in the shift categories IMPROVED, NO CHANGE and WORSENED at Weeks 8, 12 and 24, based on weekly median values, are presented in Table 11.11.

Table 11.11 Change from baseline of weekly median individual symptom score at Weeks 8, 12 and 24, FAS

Parameter	Week	Shift from baseline	Active + Active N=81		Placebo + Active N=79	
			n (%)	95% CI*	n (%)	95% CI*
Nasal Congestion Symptom Score median	8	Improved	40 (54.8%)	(42.7%, 66.5%)	34 (45.3%)	(33.8%, 57.3%)
		No change	31 (42.5%)	(31.0%, 54.6%)	38 (50.7%)	(38.9%, 62.4%)
		Worsened	2 (2.7%)	(0.3%, 9.5%)	3 (4.0%)	(0.8%, 11.2%)
	12	Improved	37 (48.1%)	(36.5%, 59.7%)	28 (38.4%)	(27.2%, 50.5%)
		No change	36 (46.8%)	(35.3%, 58.5%)	37 (50.7%)	(38.7%, 62.6%)
		Worsened	4 (5.2%)	(1.4%, 12.8%)	8 (11.0%)	(4.9%, 20.5%)
	24	Improved	34 (48.6%)	(36.4%, 60.8%)	36 (52.9%)	(40.4%, 65.2%)
		No change	28 (40.0%)	(28.5%, 52.4%)	25 (36.8%)	(25.4%, 49.3%)
		Worsened	8 (11.4%)	(5.1%, 21.3%)	7 (10.3%)	(4.2%, 20.1%)
Rhinorrhea Symptom Score median	8	Improved	26 (35.6%)	(24.7%, 47.7%)	23 (30.7%)	(20.5%, 42.4%)
		No change	39 (53.4%)	(41.4%, 65.2%)	42 (56.0%)	(44.1%, 67.5%)
		Worsened	8 (11.0%)	(4.9%, 20.5%)	10 (13.3%)	(6.6%, 23.2%)
	12	Improved	23 (29.9%)	(20.0%, 41.4%)	21 (28.8%)	(18.8%, 40.6%)
		No change	47 (61.0%)	(49.2%, 72.0%)	43 (58.9%)	(46.8%, 70.3%)
		Worsened	7 (9.1%)	(3.7%, 17.8%)	9 (12.3%)	(5.8%, 22.1%)
	24	Improved	22 (31.4%)	(20.9%, 43.6%)	22 (32.4%)	(21.5%, 44.8%)
		No change	36 (51.4%)	(39.2%, 63.6%)	44 (64.7%)	(52.2%, 75.9%)
		Worsened	12 (17.1%)	(9.2%, 28.0%)	2 (2.9%)	(0.4%, 10.2%)
Postnasal Drip Symptom Score median	8	Improved	20 (27.4%)	(17.6%, 39.1%)	13 (17.3%)	(9.6%, 27.8%)
		No change	49 (67.1%)	(55.1%, 77.7%)	48 (64.0%)	(52.1%, 74.8%)
		Worsened	4 (5.5%)	(1.5%, 13.4%)	14 (18.7%)	(10.6%, 29.3%)
	12	Improved	18 (23.4%)	(14.5%, 34.4%)	16 (21.9%)	(13.1%, 33.1%)
		No change	50 (64.9%)	(53.2%, 75.5%)	41 (56.2%)	(44.1%, 67.8%)
		Worsened	9 (11.7%)	(5.5%, 21.0%)	16 (21.9%)	(13.1%, 33.1%)
	24	Improved	16 (22.9%)	(13.7%, 34.4%)	20 (29.4%)	(19.0%, 41.7%)
		No change	42 (60.0%)	(47.6%, 71.5%)	41 (60.3%)	(47.7%, 72.0%)
		Worsened	12 (17.1%)	(9.2%, 28.0%)	7 (10.3%)	(4.2%, 20.1%)
Sneezing Symptom Score median	8	Improved	18 (24.7%)	(15.3%, 36.1%)	10 (13.3%)	(6.6%, 23.2%)
		No change	51 (69.9%)	(58.0%, 80.1%)	52 (69.3%)	(57.6%, 79.5%)
		Worsened	4 (5.5%)	(1.5%, 13.4%)	13 (17.3%)	(9.6%, 27.8%)
	12	Improved	16 (20.8%)	(12.4%, 31.5%)	12 (16.4%)	(8.8%, 27.0%)
		No change	56 (72.7%)	(61.4%, 82.3%)	47 (64.4%)	(52.3%, 75.3%)
		Worsened	5 (6.5%)	(2.1%, 14.5%)	14 (19.2%)	(10.9%, 30.1%)
	24	Improved	11 (15.7%)	(8.1%, 26.4%)	8 (11.8%)	(5.2%, 21.9%)
		No change	54 (77.1%)	(65.6%, 86.3%)	47 (69.1%)	(56.7%, 79.8%)
		Worsened	5 (7.1%)	(2.4%, 15.9%)	13 (19.1%)	(10.6%, 30.5%)

*Confidence intervals calculated using Clopper-Pearson method

The difference between treatment groups in change from baseline to each time-point has been analysed using a proportional odds model analysis as described in section 9.7.1.7.2. The results from the analyses

are presented in Table 11.12. An odds ratio above 1 indicates that two active treatments are better than one.

Table 11.12 Proportional odds analysis of individual symptom scores at Weeks 8, 12 and 24, FAS

Week	Parameter	Odds ratio*	95% CI	p-value
Week 8	Nasal Congestion Symptom Score median	1.64	0.87, 3.06	0.1222
	Rhinorrhea Symptom Score median	1.34	0.66, 2.73	0.4159
	Postnasal Drip Symptom Score median	2.16	1.08, 4.30	0.0271
	Sneezing Symptom Score median	2.06	0.91, 4.66	0.0763
Week 12	Nasal Congestion Symptom Score median	1.58	0.85, 2.92	0.1458
	Rhinorrhea Symptom Score median	1.59	0.77, 3.27	0.2110
	Postnasal Drip Symptom Score median	1.52	0.78, 2.96	0.2187
	Sneezing Symptom Score median	1.59	0.71, 3.56	0.2562
Week 24	Nasal Congestion Symptom Score median	0.77	0.41, 1.43	0.4045
	Rhinorrhea Symptom Score median	0.46	0.21, 1.01	0.0488
	Postnasal Drip Symptom Score median	0.51	0.25, 1.04	0.0603
	Sneezing Symptom Score median	1.41	0.61, 3.26	0.4206

* Odds ratio between two active treatments and one active treatment (ratio of the odds of being in the lower categories) from a proportional odds model controlling for baseline.

Two active treatments seemed to have a better effect on rhinorrhea symptom score from baseline to Weeks 8 and 12 (odds ratio 1.34 [CI: 0.66 to 2.73] and 1.59 [CI: 0.77 to 3.27], respectively). However, the difference between treatment groups was not statistically significant. At Week 24, the effect of one active treatment was significantly better as compared to two active treatments (odds ratio 0.46 [CI: 0.21 to 1.01, p1=0.0488).

The same trend was seen for the postnasal drip symptom score with two treatments being better than one at Weeks 8 and 12 (odds ratio 2.16 [CI: 1.08 to 4.30] and 1.52 [CI: 0.78 to 2.96], respectively) and a better improvement after one active treatment at Week 24 (odds ratio 0.51 [CI: 0.25 to 1.04]). The difference between treatment groups was statistically significant at Week 8 only (p_1=0.0271).

More subjects reported improvement in nasal congestion symptom score after two active treatments at Weeks 8 and 12 (odds ratio 1.64 [CI: 0.87 to 3.06] and 1.58 [CI: 0.85 to 2.92], respectively) while more subjects improved after one active treatment at Week 24 (odds ratio 0.77 [CI: 0.41 to 1.43]). No statistically significant differences were detected.

The sneezing symptom score seemed to improve in a higher proportion of subjects after two active treatments at all time-points (odds ratio 2.06 [CI: 0.91 to 4.66], 1.59 [CI: 0.71 to 3.56] and 1.41 [CI: 0.61 to 3.26] at Weeks 8, 12 and 24, respectively) although no statistically significant differences between treatment groups were detected.

Summary statistics for weekly median symptom scores and a shift category table, presenting subjects treated before the first interim analysis (“Old” Active and Low amplitude control) and after (“New” Active and Placebo) separately, are included in section 14.3.2 (Table 14.36 and Table 14.37).

11.5.4 Change in PNIF

PNIF measurements were performed at Visit 1 (screening), before treatment with the investigational device at Visit 2 (Week 0), at Visit 3 (Week 4) and at follow-up Visits 4 (Week 8) and 5 (Week 24). At each visit, three measurements were registered. For the analyses, the highest value of measurement no. 2 and 3 has been used (12).

Summary statistics, including change from baseline, are presented by treatment (*Active/Placebo*) up to Week 4 in Table 11.13 and by treatment group (*Two Active/ One Active*) to Weeks 8 and 24 in Table 11.14.

Table 11.13 Summary of PNIF (L/min) and change from baseline up to Week 4, FAS

Visit	Statistic	Active N=81	Placebo N=79
Week -1	n	81	78
Screening	Mean (SD)	118.21 (49.81)	132.12 (48.29)
	95% CI	(107.20, 129.22)	(121.23, 143.00)
	Median	110.00	130.00
	Q1, Q3	80.00, 150.00	95.00, 160.00
	Min, Max	30.0, 260.0	30.0, 300.0
Week 4	n	80	76
	Mean (SD)	126.75 (48.71)	140.79 (47.34)
	95% CI	(115.91, 137.59)	(129.97, 151.61)
	Median	125.00	130.00
	Q1, Q3	95.00, 150.00	105.00, 172.50
	Min, Max	50.0, 270.0	60.0, 270.0
Change from baseline to Week 4	n	80	75
	Mean (SD)	7.94 (34.68)	7.13 (44.41)
	95% CI	(0.22, 15.66)	(-3.08, 17.35)
	Median	10.00	10.00
	Q1, Q3	-10.00, 22.50	-30.00, 30.00
	Min, Max	-90.0, 110.0	-120.0, 140.0

The mean PNIF value ± SD at baseline (screening) was 118.21 ± 49.81 L/min (median 110.00) in the active group and 132.12 ± 48.29 L/min (median 130.00) in the Placebo group.

Based on descriptive statistics, the mean change from baseline to Week 4 was similar in the two groups; 7.94 ± 34.68 (median 10.00) in the active group and 7.13 ± 44.41 (median 10.00) among subjects treated with Placebo.

Table 11.14 Summary of PNIF (L/min) and change from baseline to Weeks 8 and 24, FAS

Week	Statistic	Active + Active N=81	Placebo + Active N=79
Week 8	n	78	75
	Mean (SD)	131.67 (49.50)	143.03 (46.99)
	95% CI	(120.51, 142.83)	(132.22, 153.84)
	Median	130.00	137.00
	Q1, Q3	95.00, 170.00	100.00, 170.00
	Min, Max	40.0, 285.0	50.0, 250.0
Change from baseline, Week 8	n	78	74
	Mean (SD)	11.86 (38.89)	9.76 (46.06)
	95% CI	(3.09, 20.63)	(-0.91, 20.43)
	Median	10.00	5.00
	Q1, Q3	-10.00, 30.00	-10.00, 30.00
	Min, Max	-90.0, 140.0	-140.0, 150.0
Week 24	n	76	75
	Mean (SD)	125.92 (49.72)	149.53 (50.92)
	95% CI	(114.56, 137.28)	(137.82, 161.25)
	Median	120.00	140.00
	Q1, Q3	90.00, 160.00	120.00, 190.00
	Min, Max	40.0, 260.0	40.0, 265.0
Change from baseline, Week 24	n	76	74
	Mean (SD)	5.59 (40.71)	16.42 (46.83)
	95% CI	(-3.71, 14.89)	(5.57, 27.27)
	Median	7.50	10.00
	Q1, Q3	-17.50, 30.00	-10.00, 40.00
	Min, Max	-120.0, 180.0	-70.0, 160.0

Based on descriptive analysis, no major difference was seen in mean change from baseline to Week 8. The mean increase from baseline to Week 24 was slightly higher among subjects receiving one active treatment only; 16.42 ± 46.83 L/min (median 10.00), as compared to 5.59 ± 40.71 L/min (median 7.50) in the Active + Active group.

11.5.5 Change in rhinosinusitis-specific quality of life, according to the SNOT-22 questionnaire

11.5.5.1 SNOT-22 summary score

The SNOT-22 questionnaire was completed by the subject at Visit 1 (baseline) before second treatment Visit 3 (Week 4) and at follow-up Visits 4 (Week 8) and 5 (Week 24), as described in section 9.5.5.1. A SNOT-22 summary score ranging from 0-110 was calculated. Higher scores represents poorer outcome.

Week 4, comparison Active/Placebo

Summary statistics for SNOT-22 summary score from baseline to Week 4 and change from baseline are presented descriptively by visit and treatment (*Active/Placebo*) in Table 11.15.

Table 11.15 Summary of SNOT-22 summary score and change from baseline to Week 4, FAS

Visit	Statistic	Active N=81	Placebo N=79
Week -1 Screening	n	81	79
	Mean (SD)	40.19 (17.03)	37.71 (15.71)
	95% CI	(36.42, 43.95)	(34.19, 41.23)
	Median	36.00	37.00
	Q1, Q3	28.00, 48.00	25.00, 50.00
	Min, Max	5.0, 95.0	7.0, 73.0
Week 4	n	80	77
	Mean (SD)	31.75 (16.55)	34.82 (15.03)
	95% CI	(28.07, 35.43)	(31.41, 38.23)
	Median	31.00	34.00
	Q1, Q3	19.50, 41.50	24.00, 44.00
	Min, Max	4.0, 78.0	6.0, 73.0
Change from baseline, Week 4	n	80	77
	Mean (SD)	-8.25 (15.60)	-2.78 (12.96)
	95% CI	(-11.72, -4.78)	(-5.72, 0.16)
	Median	-7.00	-1.00
	Q1, Q3	-16.00, 3.00	-12.00, 3.00
	Min, Max	-83.0, 17.0	-36.0, 30.0

Based on descriptive analysis, the summary score was similar in the two groups at baseline. Based on descriptive analysis, the subjects given active treatment improved more than subjects given Placebo from baseline to Week 4. The mean change from baseline to Week 4 ± SD was -8.25 ± 15.60 (median -7.00) in the Active group and -2.78 ± 12.96 (median -1.00) among subjects treated with Placebo.

Weeks 8 and 24, comparison Two Active/One Active

Summary statistics for SNOT-22 summary score from baseline to Weeks 8 and 24 and change from baseline are presented descriptively by visit and treatment group (Two Active/One Active) in Table 11.16.

Table 11.16 Summary of SNOT-22 summary score and change from baseline to Weeks 8 and 24, FAS

Week	Statistic	Active + Active N=81	Placebo + Active N=79
Week 8	n	78	75
	Mean (SD)	27.79 (15.73)	31.44 (15.66)
	95% CI	(24.25, 31.34)	(27.84, 35.04)
	Median	26.00	32.00
	Q1, Q3	16.00, 39.00	21.00, 41.00
	Min, Max	2.0, 67.0	3.0, 91.0
Change from baseline, Week 8	n	78	75
	Mean (SD)	-12.33 (14.22)	-6.84 (14.88)
	95% CI	(-15.54, -9.13)	(-10.26, -3.42)
	Median	-10.00	-4.00
	Q1, Q3	-23.00, -2.00	-16.00, 4.00
	Min, Max	-64.0, 11.0	-57.0, 23.0
Week 24	n	77	75
	Mean (SD)	31.03 (18.96)	27.63 (16.43)
	95% CI	(26.72, 35.33)	(23.85, 31.41)
	Median	29.00	28.00
	Q1, Q3	19.00, 40.00	15.00, 39.00
	Min, Max	4.0, 90.0	0.0, 78.0
Change from baseline, Week 24	n	77	75
	Mean (SD)	-9.06 (14.83)	-10.65 (17.12)
	95% CI	(-12.43, -5.70)	(-14.59, -6.71)
	Median	-9.00	-9.00
	Q1, Q3	-16.00, -1.00	-21.00, 1.00
	Min, Max	-49.0, 27.0	-73.0, 19.0

Based on descriptive analysis, the subjects given two active treatments improved more than subjects given one active treatment from baseline to Week 8. The mean change from baseline ± SD was -12.33 ± 14.22 (median -10.00) in the Two Active group and -6.84 ± 14.88 (median -4.00) among subjects treated with one active treatment.

The change from baseline to Week 24 was similar in the two groups.

11.5.5.2 SNOT-22 individual questions

Week 4, comparison Active/Placebo

Counts and percentages of subjects in each category (NO PROBLEM/VERY MILD PROBLEM/MILD OR SLIGHT PROBLEM/MODERATE PROBLEM/SEVERE PROBLEM/PROBLEM AS BAD AS IT CAN BE) up to Week 4 have been presented by treatment (Active/Placebo) for each of the SNOT-22 items separately in Table 14.38 (section 14.3.2). Number and percentage of subjects in the shift categories IMPROVED, NO CHANGE and WORSENED at Week 4 are presented in Table 14.39 (section 14.3.2). The proportion of

subjects reporting the symptom as one of the five most significant problems is presented by descriptive statistics for each item in Table 14.40 (section 14.3.2).

A higher percentage of subjects experienced improvement of symptoms at Week 4 after active treatment, as compared to Placebo, for 19/22 items. The treatment groups differed most as regards "*Difficulty falling asleep"* (38.8%/23.4%; Active/Placebo) followed by *"Blockage/congestion of nose"* (51.3%/36.4%; Active/Placebo) (Table 14.39).

A higher percentage of subjects treated with Placebo experienced worsening of symptoms, as compared to active treatment, for 19/22 items. The two groups differed most as regards "*Need to blow nose"* (12.5%/28.6%; Active/Placebo), "*Runny nose"* (18.8%/32.5% ;Active/Placebo) and *"Fatigue*" (17.5%/29.9% ;Active/Placebo) (Table 14.39).

The three items assessed as one of the five most significant problems at screening by the highest percentage of subjects in the Active group were *"Blockage/congestion of nose"* (96.3%), *"Need to blow nose"* (43.2%) and *"Lack of good night's sleep"* (35.8%). The corresponding items in the Placebo group were *"Blockage/congestion of nose"* (92.4%), *"Waking up tired"* (41.8%) and *"Need to blow nose"* (36.7%). *"Blockage/congestion of nose*" was slightly more improved at Week 4 (reported as one of the five most significant problems by fewer subjects) after active treatment (87.5%) as compared to Placebo (90.9%). *"Need to blow nose"* was reported by an increased number of subjects at Week 4 in both groups (45.0% /37.7%; Active/Placebo) (Table 14.40).

Weeks 8 and 24, comparison Two Active/One Active

Counts and percentages of subjects in each category at Weeks 8 and 24 are presented by treatment group (Two Active/One Active) for each of the SNOT-22 items separately in Table 14.41. Number and percentage of subjects in the shift categories IMPROVED, NO CHANGE and WORSENED at Weeks 8 and 24 are presented in Table 14.42. The proportion of subjects reporting the symptom as one of the five most significant problems is presented by descriptive statistics for each item in Table 14.43 (section 14.3.2).

At Week 8, improvement was seen in a higher percentage of subjects after two active treatments as compared to one active treatment for 17/22 items. The treatment groups differed most as regards *"Need to blow nose"* (61.5% /41.3%; Two Active/One Active), "*Frustrated/restless/irritable"* (44.9%/26.7%; two active/one active) and *"Thick nasal discharge"* (47.4% /32.0%; Two Active/One Active).

For 20/22 items, worsening of symptoms was reported by more subjects after one active treatment, as compared to two active treatments. The treatment groups differed most as regards "*Frustrated/restless/irritable"* (12.8% /30.7%; Two Active/One Active), *"Need to blow nose"* (11.5%/29.3%; Two Active/One Active) and *"Dizziness"* (9.0% /24.0%; Two Active/One Active) (Table 14.42).

The three items most frequently assessed as one of the five most significant problems in both groups were "*Blockage/congestion of nose*" (80.8% /86.7%; Two Active/One Active), "*Need to blow nose"*

(34.6% /41.3%; Two Active/One Active) and *"Waking up tired"* (38.5 /44.0%; Two Active/One Active) (Table 14.43).

At Week 24, improvement was seen in a higher percentage of subjects after two active treatments as compared to one for 8/22 items. The treatment groups differed most as regards "*Thick nasal discharge"* (42.9%/30.7%; Two Active/One Active).

Worsening of symptoms was reported by more subjects after one active treatment, as compared to two active treatments for 12/22 items (Table 14.42).

The three items most frequently assessed as one of the five most significant problems in the group receiving two active treatments were "*Blockage/congestion of nose*" (88.3%), "*Need to blow nose"* (37.7%) and *"Post-nasal discharge* (35.1%). Corresponding items and percentages for the One Active treatment group were "*Blockage/congestion of nose*" (85.3%), *"Waking up tired"* (34.7%) and "*Need to blow nose"* (33.3%) (Table 14.43).

11.5.6 Change in functional disability and health-related quality of life, according to the EQ-5D-3L questionnaire

The EQ-5D-3L questionnaire was completed by the subject at screening (baseline), before treatment with the investigational device at Week 0 and Week 4 and at follow-up visits at Week 8 and Week 24 (see section 9.5.5.2).

Up to Week 4, comparison Active/Placebo

Number and percentages of subjects in each severity level (no problems/some or moderate problems/extreme problems) for each of the five EQ-5D-3L dimensions are presented by visit and treatment from baseline up to Week 4 in Table 14.44 (section 14.3.2).

Number and percentage of subjects in the shift categories IMPROVED, NO CHANGE and WORSENED, based on the severity levels, are presented by week and treatment in Table 11.17.

Table 11.17 EQ-5D-3L change from baseline up to Week 4, FAS

Parameter	Week	Shift from baseline	Active N=81		Placebo N=79	
			n (%)	95% CI*	n (%)	95% CI*
Mobility	Week 4	Improved	1 (1.3%)	(0.0%, 6.8%)	2 (2.6%)	(0.3%, 9.1%)
		No change	78 (97.5%)	(91.3%, 99.7%)	73 (94.8%)	(87.2%, 98.6%)
		Worsened	1 (1.3%)	(0.0%, 6.8%)	2 (2.6%)	(0.3%, 9.1%)
Self-Care	Week 4	Improved	0	(0.0%, 4.5%)	0	(0.0%, 4.7%)
		No change	80 (100.0%)	(95.5%, 100.0%)	77 (100.0%)	(95.3%, 100.0%)
		Worsened	0	(0.0%, 4.5%)	0	(0.0%, 4.7%)
Usual Activities	Week 4	Improved	1 (1.3%)	(0.0%, 6.8%)	2 (2.6%)	(0.3%, 9.1%)
		No change	77 (96.3%)	(89.4%, 99.2%)	73 (94.8%)	(87.2%, 98.6%)
		Worsened	2 (2.5%)	(0.3%, 8.7%)	2 (2.6%)	(0.3%, 9.1%)
Pain/Discomfort	Week 4	Improved	11 (13.8%)	(7.1%, 23.3%)	6 (7.8%)	(2.9%, 16.2%)
		No change	57 (71.3%)	(60.0%, 80.8%)	58 (75.3%)	(64.2%, 84.4%)
		Worsened	12 (15.0%)	(8.0%, 24.7%)	13 (16.9%)	(9.3%, 27.1%)
Anxiety/Depression	Week 4	Improved	11 (13.8%)	(7.1%, 23.3%)	3 (3.9%)	(0.8%, 11.0%)
		No change	63 (78.8%)	(68.2%, 87.1%)	68 (88.3%)	(79.0%, 94.5%)
		Worsened	6 (7.5%)	(2.8%, 15.6%)	6 (7.8%)	(2.9%, 16.2%)

* Confidence intervals calculated using Clopper-Pearson method

Based on descriptive analysis, a majority of the subjects in both groups (≥94.8%) experienced no change from baseline to Week 4 as regards *"Mobility"*, *"Self-care"* and *"Usual activities"*. An improvement of "*Pain/discomfort"* from baseline to Week 4 was experienced by 11 subjects (13.8%) given active treatment and by 6 subjects (7.8%) treated with Placebo. For *Anxiety/Depression*, an improvement from baseline was seen in 11 (13.8%) and 3 (3.9%) of the subjects in the Active and Placebo group, respectively.

Descriptive statistics for EQ VAS up to Week 4, including change from baseline, are presented in Table 14.45 (section 14.3.2). The mean VAS score at baseline ±SD was 77.65 ± 13.91 (median 80.00) in the Active group and 81.24 ± 14.25 (median 82.00) in the Placebo group. No notable change from baseline to Week 4 was seen for any of the groups.

Weeks 8 and 24, comparison Two Active/One Active

Number and percentages of subjects in each severity level (no problems/some or moderate problems/extreme problems) for each of the five EQ-5D-3L dimensions at Weeks 8 and 24 are presented by visit and treatment group in Table 14.46 (section 14.3.2). Number and percentage of subjects in the shift categories IMPROVED, NO CHANGE and WORSENED, based on the severity levels, are presented by week and treatment in Table 11.18.

Table 11.18 EQ-5D-3L change from baseline to Week 8 and 24, FAS

Parameter	Week	Shift from baseline	Active + Active N=81		Placebo + Active N=79	
			n (%)	95% CI*	n (%)	95% CI*
Mobility	Week 8	Improved	0	(0.0%, 4.6%)	1 (1.3%)	(0.0%, 7.2%)
		No change	78 (100.0%)	(95.4%, 100.0%)	74 (98.7%)	(92.8%, 100.0%)
		Worsened	0	(0.0%, 4.6%)	0	(0.0%, 4.8%)
	Week 24	Improved	0	(0.0%, 4.7%)	2 (2.7%)	(0.3%, 9.3%)
		No change	74 (96.1%)	(89.0%, 99.2%)	70 (93.3%)	(85.1%, 97.8%)
		Worsened	3 (3.9%)	(0.8%, 11.0%)	3 (4.0%)	(0.8%, 11.2%)
Self-Care	Week 8	Improved	0	(0.0%, 4.6%)	0	(0.0%, 4.8%)
		No change	78 (100.0%)	(95.4%, 100.0%)	75 (100.0%)	(95.2%, 100.0%)
		Worsened	0	(0.0%, 4.6%)	0	(0.0%, 4.8%)
	Week 24	Improved	0	(0.0%, 4.7%)	1 (1.3%)	(0.0%, 7.2%)
		No change	77 (100.0%)	(95.3%, 100.0%)	74 (98.7%)	(92.8%, 100.0%)
		Worsened	0	(0.0%, 4.7%)	0	(0.0%, 4.8%)
Usual Activities	Week 8	Improved	1 (1.3%)	(0.0%, 6.9%)	2 (2.7%)	(0.3%, 9.3%)
		No change	76 (97.4%)	(91.0%, 99.7%)	72 (96.0%)	(88.8%, 99.2%)
		Worsened	1 (1.3%)	(0.0%, 6.9%)	1 (1.3%)	(0.0%, 7.2%)
	Week 24	Improved	1 (1.3%)	(0.0%, 7.0%)	3 (4.0%)	(0.8%, 11.2%)
		No change	73 (94.8%)	(87.2%, 98.6%)	70 (93.3%)	(85.1%, 97.8%)
		Worsened	3 (3.9%)	(0.8%, 11.0%)	2 (2.7%)	(0.3%, 9.3%)
Pain/Discomfort	Week 8	Improved	15 (19.2%)	(11.2%, 29.7%)	10 (13.3%)	(6.6%, 23.2%)
		No change	56 (71.8%)	(60.5%, 81.4%)	57 (76.0%)	(64.7%, 85.1%)
		Worsened	7 (9.0%)	(3.7%, 17.6%)	8 (10.7%)	(4.7%, 19.9%)
	Week 24	Improved	9 (11.7%)	(5.5%, 21.0%)	13 (17.3%)	(9.6%, 27.8%)
		No change	55 (71.4%)	(60.0%, 81.2%)	55 (73.3%)	(61.9%, 82.9%)
		Worsened	13 (16.9%)	(9.3%, 27.1%)	7 (9.3%)	(3.8%, 18.3%)
Anxiety/Depression	Week 8	Improved	7 (9.0%)	(3.7%, 17.6%)	3 (4.0%)	(0.8%, 11.2%)
		No change	65 (83.3%)	(73.2%, 90.8%)	66 (88.0%)	(78.4%, 94.4%)
		Worsened	6 (7.7%)	(2.9%, 16.0%)	6 (8.0%)	(3.0%, 16.6%)
	Week 24	Improved	7 (9.1%)	(3.7%, 17.8%)	4 (5.3%)	(1.5%, 13.1%)
		No change	61 (79.2%)	(68.5%, 87.6%)	62 (82.7%)	(72.2%, 90.4%)
		Worsened	9 (11.7%)	(5.5%, 21.0%)	9 (12.0%)	(5.6%, 21.6%)

* Confidence intervals calculated using Clopper-Pearson method

Based on descriptive analysis, a majority of the subjects in both treatment groups (≥93.3%) experienced no change from baseline to Weeks 8 and 24 as regards *"Mobility", "Self-care"* and *"Usual activities".*

An improvement of *"Pain/discomfort"* was reported both by subjects given two active treatments (15 subjects [19.2%] at Week 8 and by 9 subjects [11.7%] at Week 24) and by subjects given one active treatment (10 subjects [13.3%] at Week 8 and 13 subjects [17.3%] at Week 24.

An improvement was also reported for the domain *"Anxiety/depression"* by subjects given two active treatments (7 subjects [9.0%] at Week 8 and 7 subjects [9.1%] at Week 24) and by subjects given one active treatment (3 subjects [4.0%] at Week 8 and 4 subjects [5.3%] at Week 24.

Descriptive statistics for EQ VAS at Weeks 8 and 24, including change from baseline, are presented in Table 14.47 (section 14.3.2). Only minor changes from baseline were seen at Weeks 8 and 24. After two active treatments, an improvement in mean scores of 3.35 ± 8.73 (median 3.00) was noted at Week 8, as compared to a minor increase of 0.95 ± 10.17 (median 0.00) after one active treatment.

11.5.7 Use of rescue medication

Descriptive statistics of the cumulative number of days with rescue medication during participation in the clinical investigation is presented in Table 11.19.

Table 11.19 Number of days with rescue medication, FAS

	Statistic	Active N=81	Placebo N=79
Used rescue medication during study	**n (%)**	**27 (33.3%)**	**28 (35.4%)**
Baseline	n	81	79
	Mean (SD)	0.7 (1.7)	0.8 (1.8)
	95% CI for the mean	(0.3, 1.1)	(0.4, 1.2)
	Median	0.0	0.0
	Q1, Q3	0.0, 0.0	0.0, 0.0
	Min, Max	0, 6	0, 7
From baseline to Week 4 (Visit 2)	n	81	79
	Mean (SD)	2.4 (6.0)	2.8 (6.3)
	95% CI for the mean	(1.0, 3.7)	(1.4, 4.3)
	Median	0.0	0.0
	Q1, Q3	0.0, 1.0	0.0, 2.0
	Min, Max	0, 27	0, 25
From Week 4 to Week 8 (Visit 3)	n	81	79
	Mean (SD)	1.6 (5.4)	2.4 (6.6)
	95% CI for the mean	(0.4, 2.8)	(0.9, 3.9)
	Median	0.0	0.0
	Q1, Q3	0.0, 0.0	0.0, 0.0
	Min, Max	0, 28	0, 32
From Week 9 (after Visit 3)	n	81	79
	Mean (SD)	0.8 (2.3)	1.0 (3.4)
	95% CI for the mean	(0.3, 1.3)	(0.2, 1.7)
	Median	0.0	0.0
	Q1, Q3	0.0, 0.0	0.0, 0.0
	Min, Max	0, 11	0, 21

The mean number of days with rescue medication was similar in both treatment groups at baseline (0.7 days [CI: 0.3 to 1.1] / 0.8 days [CI: 0.4 to 1.2]; Active/Placebo). During the 4 weeks following the first treatment the mean number of days with rescue medication was slightly increased in both groups (2.4 days [CI: 1.0 to 3.7] / 2.8 days [CI: 1.4 to 4.3]; Active/Placebo). During the 4 weeks following the second treatment the mean number of days was somewhat higher in the Placebo group (2.4 days [CI: 0.9 to 3.9]) as compared to the Active treatment group (1.6 days [CI: 0.4 to 2.8]).

11.5.8 Statistical/Analytical Issues

11.5.8.1 Adjustments for Covariates

Adjustment for baseline value has been performed in the analysis, if assessed. It was planned to include site as a covariate in the analyses. However, since two sites had included subjects in the first period only ("Old" Active and Low amplitude control groups) only and two sites in the second ("New" Active and Placebo groups), site was not included in the models.

11.5.8.2 Handling of Dropouts or Missing Data

Outliers have been included in summary tables and listings and have not been handled separately. Available data from prematurely withdrawn subjects have been included in the analysis as far as possible.

11.5.8.3 Interim Analyses and Data Monitoring

An interim analysis with the aim to achieve safety and efficacy interim data to be used for strategy and design of future investigations was performed when 48 subjects were randomized to Low amplitude control treatment and 49 to active treatment. A total of 91 subjects, 47 in the Active and 44 in the Low amplitude control group had a Visit 2 performed before the cut-off date of 2013-06-20 and were thus included in the analysis. The results from this analysis indicated that the Low amplitude control procedure might have an effect. The Low amplitude control procedure was therefore modified to just insert the balloon into the nostrils without neither inflating the catheter nor stimulating the mucosa by oscillations (Placebo). The sample size was re-calculated as described in sections 9.7.2 and 9.8.1.3.

Since the option to include a Placebo group and not include additional subjects in the Low amplitude control group was not planned in advance, it was decided to perform a second interim analysis when at least 50% of the Placebo subjects were estimated to have completed Visit 3 (Week 4). The cut-off date for the second interim analysis was set to 2013-12-16 and data from subjects having a weekly mean TVRSS value at Week 4 on the cut-off date were included in the analysis. The analysis included 65 subjects in the Active group and 41 subjects in the Placebo group.

The results from the two interim analyses are included in Appendix 16.1.7.

11.5.8.4 Multicentre Studies

It was planned to include site as a covariate in the analyses. However, since two sites had included subjects in the first period only ("Old" Active and Low amplitude control groups) only and two sites in the second ("New" Active and Placebo treatment groups), site was not included in the models.

11.5.8.5 Multiple Comparison/Multiplicity

Since the interim analyses results were not expected to affect the course of the study no multiplicity adjustment was to be performed. The aim of the interim analysis was to achieve safety and efficacy/performance interim data to be used for strategy and design of future studies.

However, the results of the interim analysis indicated that the Low amplitude control procedure might have an effect. It was therefore decided to modify the Low amplitude control to avoid stimulation, i.e. neither to inflate the catheter nor to stimulate the mucosa by oscillations.

The option to include a Placebo group and not include additional subjects in the Low amplitude control group was not planned in advance. Although this was an exploratory study, it is still important to be aware that inflation of the Type I error rate or biased estimates may occur in the results of exploratory studies which, when unrecognized, can lead to counterproductive design decisions for future studies.

11.5.8.6 Use of an "efficacy/performance Subset" of subjects

The FAS is considered as the primary analysis dataset, and has been used for all primary and secondary performance analyses. The PPAS has been used for the efficacy/performance analysis to investigate the sensitivity of the results on weekly mean TVRSS from the FAS analysis.

11.5.8.7 Examination of Subgroups

The analysis of the primary endpoint has been performed also by sex (males, females), type of diagnosis (non-allergic rhinitis, rhinitis medicamentosa, combination) and age (18 - <35, 35 - <50, 50-65).

11.5.9 Tabulation of Individual Response

Individual subject data listings as regards efficacy response data are included in Appendix 16.2.6.

11.5.10 By-Patient Displays

Not applicable.

11.5.11 Efficacy/performance Conclusions

<u>Primary efficacy/performance</u>

The weekly mean TVRSS decreased significantly more from baseline to Week 4 in the Active group as compared to Placebo in the FAS population (p=0.0531). The significant result for the FAS was supported by the difference detected for the PPAS population (p=0.0349).

Statistically significant differences between Active and Placebo in change from baseline to Week 4 in weekly mean TVRSS were found when analysing the subgroups females (p=0.0471), age group 50-65 years (p=0.0515) and subjects with non-allergic rhinitis (p=0.0213).

Secondary efficacy/performance

TVRSS at Weeks 8-24

The improvement of weekly mean TVRSS from baseline to Week 8 was significantly better after two active treatments as compared to one active treatment (p=0.0109 in FAS and p=0.0190 in PPAS).

Individual symptom score

A significantly better improvement (more subjects shifting to a lower score) after active treatment as compared to Placebo, based on weekly median symptom scores, was seen at Week 4 for the nasal congestion symptom score (odds ratio 2.49 [CI: 1.29 to 4.82], p=0.0056).

Two active treatments had a better effect on postnasal drip symptom score at Week 8 (odds ratio 2.16 [CI: 1.08 to 4.30], p=0.0271), as compared to one active treatment. At Week 24, a significantly higher proportion of subjects reported improvement of rhinorrhea symptom score after one active treatment, as compared to two active treatments (odds ratio 0.46 [CI: 0.21 to 1.01], p=0.0488).

PNIF

Based on descriptive analysis of mean PNIF values, no major difference was seen in change from baseline up to Week 8. The mean increase from baseline to Week 24 was slightly higher among subjects receiving one active treatment only; 16.42 ± 46.83 L/min (median 10.00), as compared to 5.59 ± 40.71 L/min (median 7.50) after two active treatments.

SNOT-22

Based on descriptive analysis of SNOT-22 summary score, the subjects given active treatment improved more than subjects given Placebo from baseline to Week 4. Subjects treated with two active treatments had a higher reduction in SNOT-22 summary score at Week 8 as compared to subjects given one active treatment.

EQ-5D-3L

Based on descriptive analysis, an improvement of "*Pain/discomfort*" and "*Anxiety/Depression*" from baseline to Week 4 was experienced by a higher percentage of subjects after active treatment, as compared to Placebo. "*Pain/discomfort*" seemed to improve more frequently after two active treatments at Week 8 and after one active treatment at Week 24. A higher percentage of subjects experienced improvement of "*Anxiety/Depression*" after two active treatments at Weeks 8 and 24. No notable changes from baseline to Weeks 4, 8 or 24 in EQ VAS were seen for any of the groups.

Use of rescue medication

The mean number of days with rescue medication was similar in both treatment groups at baseline, slightly increased in both groups during the 4 weeks following the first treatment and somewhat higher

in the Placebo group as compared to the active treatment group during the 4 weeks following the second treatment.

12 SAFETY EVALUATION

12.1 Extent of exposure

A total of 207 subjects received the first of two planned treatments (Visit 2). The Low amplitude control treatment was administered to 47 subjects, the Placebo was used for 79 subjects and 81 subjects were given active treatment. Of the 207 subjects treated at Visit 2, 199 subjects were given active treatment at Visit 3 (second treatment).

12.2 Adverse Events (AEs)

12.2.1 Brief Summary of AEs

A summary of AEs experienced by the investigational subjects during the investigation is given in Table 14.48 (section 14.4.1). A total of 226 events were experienced by 120 subjects (58.8%) whereof 21 events, reported by 20 subjects (9.7%), were assessed as being related to the investigational procedure Eleven (11) of these procedure-related events were also assessed as being related to the investigational device.

AEs experienced after first treatment up to Week 4, prior to the second treatment, are summarized by treatment (*Active/Placebo*) in Table 12.1.

Table 12.1 Overview of AEs up to second treatment (Week 4), Safety analysis set

Event	Active N=81		Low amplitude control N=47		Placebo N=79		Total N =207	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
AEs	22 (27.2%)	30	8 (17.0%)	10	31 (39.2%)	45	61 (29.5%)	85
SAEs	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
ADEs[1]	3 (3.7%)	3	1 (2.1%)	1	3 (3.8%)	3	7 (3.4%)	7
SADEs[1]	0	0	0	0	0	0	0	0
Causality (relationship to investigational device)[2]								
Not related to device	21 (95.5%)	29	8 (100.0%)	9	30 (96.8%)	44	59 (96.7%)	82
Related to device[3]	1 (4.5%)	1	1 (12.5%)	1	1 (3.2%)	1	3 (4.9%)	3
Severity[2]								
Mild	17 (77.3%)	25	2 (25.0%)	3	19 (61.3%)	29	38 (62.3%)	57
Moderate	5 (22.7%)	5	4 (50.0%)	5	12 (38.7%)	15	21 (34.4%)	25
Severe	0	0	2 (25.0%)	2	1 (3.2%)	1	3 (4.9%)	3

n = number of subjects. Percentages are based on the number of subjects within each treatment group

AEs with partially missing start date were calculated as starting before second treatment

[1]Events related to the investigational procedure

[2] Percentages are based on the total number of AEs within each treatment group.

[3]Procedure related events which are also assessed as being device-related

The total number of events during the period following the first treatment was 85, experienced by 61 subjects (29.5%). A higher number of AEs occurred in the Placebo group as compared to the two other groups. Thirty-one (31) subjects (39.2%) treated with Placebo experienced a total of 45 AEs, as compared to 22 subjects (27.2%) reporting 30 events among subjects given active treatment and 8 subjects (17.0%) reporting 10 events in the Low amplitude control group.

A total of 7 events were assessed as related to the investigational procedure whereof 3 were also assessed as related to the device. Two events were assessed as severe but not related in the Low amplitude control group. One (1) event (increased upper airway secretion) experienced by a subject given Placebo (SE0283) was assessed as severe and related to study device.

One SAE (stroke) assessed as not related to the investigational device or procedures occurred in the Low amplitude control group. The subject (SE 0216) was withdrawn due to the SAE (see section 12.4.1 and Appendix 16.2.7). One non-serious AE in the same group (epilepsy; subject SE0315), assessed as not related to the device but to the procedure, led to withdrawal. No other subjects were withdrawn due to AEs.

A summary of AEs experienced after second treatment (from Week 4) is given by treatment group (Two Active/One Active) in Table 12.2. All subjects were given active treatment at this visit.

Table 12.2 Overview of adverse Events from Week 4, Safety analysis set

Event	Active + Active N=81		Low amplitude control + Active N=47		Placebo + Active N=79		Total N=207	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
AEs	34 (42.0%)	47	12 (25.5%)	13	45 (57.0%)	81	91 (44.0%)	141
SAEs	0	0	0	0	0	0	0	0
ADE[1]	4 (4.9%)	4	2 (4.3%)	2	7 (8.9%)	8	13 (6.3%)	14
SADEs[1]	0	0	0	0	0	0	0	0
Causality (relationship to investigational device)[2]								
Not related to device	33 (97.1%)	45	11 (91.7%)	12	43 (95.6%)	76	87 (95.6%)	133
Related to device[3]	2 (5.9%)	2	1 (8.3%)	1	5 (11.1%)	5	8 (8.8%)	8
Severity[2]								
Mild	22 (64.7%)	30	8 (66.7%)	8	26 (57.8%)	55	56 (61.5%)	93
Moderate	14 (41.2%)	17	5 (41.7%)	5	22 (48.9%)	24	41 (45.1%)	46
Severe	0	0	0	0	2 (4.4%)	2	2 (2.2%)	2

n = number of subjects., Percentages are based on the number of subjects within each treatment group

AEs with partially missing start date were calculated as starting before second treatment

[1]Events related to the investigational procedure

[2] Percentages are based on the total number of AEs within each treatment group.

[3]Procedure related events which are also assessed as being device-related

The total number of events during the period following the first treatment was 141, experienced by 91 subjects (44.0%). More AEs occurred in the Placebo + Active group as compared to the two other groups. Forty-five (45) subjects (57.0%) treated with Placebo + Active experienced a total of 81 AEs during the period following the second treatment (active), as compared to 34 subjects (42.0%) reporting 47 events among subjects given two active treatments and 12 subjects (25.5%) reporting 13 events in the Low amplitude control + Active group.

Two events in 2 subjects (4.4%) in the Placebo + Active group were assessed as severe and related to the investigational device (sneezing, lightheaded). A total of 14 events were assessed as procedure related whereof 8 were also assessed as related to the device. Slightly more events related to the device or procedure occurred in the Placebo + Active group as compared to the Active+ Active group.

No SAEs occurred after the second treatment given at Week 4.

12.2.2 Display of AEs

Incidence of AEs by MedDRA SOC and PT are presented as number and percentage of subjects and number of mentions by treatment/treatment group for the entire study period in Table 14.49, for the period following the first treatment (up to Week 4) in Table 14.50 and from second treatment (Week 4) to end of study in Table 14.51 (section 14.4.1).

The AEs presented in the CIP as anticipated during the insertion of the catheter in the nasal cavity or during treatment with the investigational device have been presented separately in Table 12.3 (up to Week 4) and in Table 12.4 (from Week 4). These ADEs were only to be reported in the AE section of the e-CRF if assessed as moderate or severe. The tables below include all anticipated AEs (mild, moderate and severe).

Table 12.3 Anticipated AEs reported at first treatment (Week 0), Safety analysis set

	Active N=81		Low amplitude control N=47		Placebo N=79		Total N =207	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Any anticipated AE	37 (45.7%)	37	12 (25.5%)	12	17 (21.5%)	17	66 (31.9%)	66
Sneezing	11 (13.6%)	11	0	0	2 (2.5%)	2	13 (6.3%)	13
Increased nasal secretion	17 (21.0%)	17	6 (12.8%)	6	3 (3.8%)	3	26 (12.6%)	26
Increased tear secretion	24 (29.6%)	24	6 (12.8%)	6	8 (10.1%)	8	38 (18.4%)	38
Paraesthesia of the lip	5 (6.2%)	5	2 (4.3%)	2	2 (2.5%)	2	9 (4.3%)	9
Slight pain	7 (8.6%)	7	4 (8.5%)	4	4 (5.1%)	4	15 (7.2%)	15
Slight discomfort	11 (13.6%)	11	4 (8.5%)	4	3 (3.8%)	3	18 (8.7%)	18
Mild burning sensation	2 (2.5%)	2	1 (2.1%)	1	0	0	3 (1.4%)	3
Minor epistaxis (at withdrawal of catheter)	6 (7.4%)	6	0	0	2 (2.5%)	2	8 (3.9%)	8

Table 12.4 Anticipated AEs reported at second treatment (Week 4), Safety analysis set

	Active + Active N=81		Low amplitude control + Active N=47		Placebo + Active N=79		Total N =207	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Any anticipated AE	44 (54.3%)	44	17 (36.2%)	17	58 (73.4%)	58	119 (57.5%)	119
Sneezing	16 (19.8%)	16	4 (8.5%)	4	13 (16.5%)	13	33 (15.9%)	33
Increased nasal secretion	24 (29.6%)	24	14 (29.8%)	14	22 (27.8%)	22	60 (29.0%)	60
Increased tear secretion	27 (33.3%)	27	11 (23.4%)	11	35 (44.3%)	35	73 (35.3%)	73
Paraesthesia of the lip	6 (7.4%)	6	2 (4.3%)	2	9 (11.4%)	9	17 (8.2%)	17
Slight pain	4 (4.9%)	4	4 (8.5%)	4	11 (13.9%)	11	19 (9.2%)	19
Slight discomfort	9 (11.1%)	9	5 (10.6%)	5	25 (31.6%)	25	39 (18.8%)	39
Mild burning sensation	5 (6.2%)	5	1 (2.1%)	1	2 (2.5%)	2	8 (3.9%)	8
Minor epistaxis (at withdrawal of catheter)	3 (3.7%)	3	0	0	3 (3.8%)	3	6 (2.9%)	6

12.2.3 Analysis of AEs

After the first treatment, the SOC most frequently represented in all groups was *Infections and infestations*, followed by N*ervous system disorders* and Respiratory, *thoracic and mediastinal disorders*. Of the subjects treated with Placebo, 17.7% reported events within *Infections and infestations* as compared to 12.3% and 8.5% of the subjects treated with active treatment and the Low amplitude

control, respectively. The most frequently reported event was nasopharyngitis, reported 16.5% of the subjects treated with Placebo as compared to 8.6% and 6.4% of the subjects treated with active treatment and the Low amplitude control, respectively. Of the events related to N*ervous system disorders*, migraine was reported for 3 (3.7%) of the subjects given active treatment and for none of the subjects treated with Placebo or Low amplitude control. Headache was reported by 4 subjects in the Active group and the Placebo group, respectively (Table 14.50).

Following the second treatment (from Week 4 to end of study) the SOC most frequently represented in all groups was still *Infections and infestations*, followed by *Respiratory, thoracic and mediastinal disorders* and N*ervous system disorders*. For these SOCs, more events were reported in the Placebo + Active group as compared to the two other groups. Nasopharyngitis was the most frequently reported event, reported by 34.2% of the subjects treated with Placebo and one active treatment as compared to 23.5% of the subjects given two active treatments and 8.5% of the subjects in the Low amplitude control + Active group. Migraine was reported by two subjects (2.5%) given two active treatments as compared to none in the other two groups. Seventeen (17) events of headache were reported by 8 subjects (10.1%) in the Placebo + Active group (Table 14.51).

A total of 185 events pre-defined as anticipated occurred during the insertion of the catheter in the nasal cavity or during treatment with the investigational device. Of these events, 66 occurred after first treatment and 119 were reported after the second treatment. Eight (8) of the anticipated events reported were assessed as moderate or severe and thus reported as AEs. The remaining 177 anticipated events were assessed s mild. At the first treatment visit, a higher percentage of subjects reported anticipated AEs after active treatment (37 subjects [45.7%]) as compared to subjects treated with the Low amplitude control (12 subjects [25.5%]) and Placebo (17 subjects [21.5%]). Overall, *Increased tear secretion*, *Increased nasal secretion* and *Slight discomfort* were the three most frequently reported events. All anticipated events reported occurred more frequently in the Active group (Table 12.3).

At Visit 3 (all subjects given active treatment) anticipated AEs were most frequently reported in the Placebo + Active group (58 subjects [73.4%]), as compared to subjects treated with two active treatments (44 subjects [54.3%] and the Low amplitude control (17 subjects [36.2%]). Overall, *Increased tear secretion*, *Increased nasal secretion* and *Slight discomfort* were still the three most frequently reported events with *Increased tear secretion* and *Slight discomfort* being more common in the Placebo + Active group (35 subjects [44.3%] and 25 subjects [31.6%] respectively) (Table 12.4).

12.2.4 Listing of AEs by subject

Listings of all individual subject AE data are included in Appendix 16.2.7.1.

12.3 Device deficiencies

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of the investigational medical device (including malfunctions, use errors, and inadequate labelling) were reported in the e-CRF (see listing in Appendix 16.2.7.8). A total of 17 events of device deficiencies were reported. None of these were reported as an AE. Fifteen (15) of the events were due to malfunction of

the device and 2 to use error. Use of the device was discontinued due to the reported deficiency in two cases.

12.4 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

One SAE occurred in this investigation. No deaths or other significant AEs were reported.

12.4.1 Narratives of Serious Adverse Events

Subject SE0216

The event occurred to a 64 year old male subject. The start date of the event was 2013-05-22 and the stop date was 2013-06-13. Investigational treatment with the Low amplitude control was given on 2013-05-14 (Visit 2). The subject experienced a stroke with acute vertigo and problems with balance and speaking problems. He visited the emergency department at Malmö Hospital and treatment was initiated. The subject mentioned at the follow up visit that they found a defect between left and right heart chamber by ultrasound. This was not previously known by the subject and probably he had had it from birth. This was considered to be the cause of an embolus that was transported to the brain causing a cerebral ischemia. The event resulted in hospitalisation. The Investigator classified the event as severe but not related to the investigational device or procedures. The subject was withdrawn from participation in the investigation and did not receive the second treatment.

12.5 CLINICAL LABORATORY EVALUATION

No clinical laboratory assessments were performed.

12.6 Vital signs, physical findings and other observations related to safety, and other observations related to safety

No clinical safety evaluations other than AE reporting were performed.

12.7 Safety conclusions

The total number of events during the investigation was 226 events experienced by 120 subjects (58%), whereof 21 events, reported by 20 subjects (9.7%), were assessed as being related to the investigational procedure. Eleven (11) of these procedure-related events were also assessed as being related to the investigational device. A higher number of AEs occurred after treatment with Placebo as compared to active treatment and Low amplitude control after the first treatment. During the period following the second treatment (active treatment given to all subjects), more AEs occurred in the Placebo + Active group as compared to the two other groups. A majority of AEs were assessed as not related to the investigational device or to clinical investigational procedures in all treatment groups. One SAE (stroke), assessed as not related to the investigational device or procedures, occurred in the Low amplitude control group two weeks after the first treatment.

Anticipated AEs showed to be more frequently reported in relation to active treatment as compared to the Low amplitude control and Placebo with *Increased tear secretion*, *Increased nasal secretion* and *Slight discomfort* being the most frequently reported events.

13 DISCUSSION AND OVERALL CONCLUSIONS

The aim of this interventional, multi-centre, double-blinded, placebo-controlled investigation was to investigate if kinetic oscillations stimulation applied to the nasal mucosa surface, administered using the PBASE system, could reduce rhinitis symptoms in patients with idiopathic rhinitis. Male and female patients, 18-65 years of age, with persistent (>12 weeks) symptoms of idiopathic rhinitis dominated by nasal congestion were considered for participation. A total of 207 male and female subjects with a mean age of 47 years were randomized and treated with either active treatment or Low amplitude control/Placebo at the first treatment visit (Visit 2) and 199 of these subjects were also given an active treatment at Visit 3. Of the subjects randomized, 37 subjects were later excluded from the PPAS, most of them for not having a nasal congestion symptom score median ≥2 at inclusion and thus being defined as major CIP violators.

Due to the modification of the control procedure after the interim analysis and the re-calculated sample size approx. 60% of the subjects given active treatment were recruited during April and May while the Placebo group, used as comparator in the main efficacy/performance analyses, were recruited during September – February with 55.7% being treated during November and December. However, when looking at descriptive results for the primary endpoint (change from baseline to Week 4 in TVRSS) presented by treatment group before and after the interim analysis, no major differences are seen between the two active groups (recruited before and after the interim analysis).

The average intensity of nasal symptoms during the previous 24 hours was registered by the subjects in the electronic diary from screening to last follow-up. The primary endpoint was calculated based on weekly mean TVRS scores. One active treatment with the PBASE system had a significantly better effect on symptoms, according to TVRSS, than Placebo when measured four weeks after the first treatment in both FAS and PPAS. Females showed to be better responders than males and patients with non-allergic rhinitis responded better than patients with rhinitis medicamentosa or a combination diagnosis. Of the age groups tested patients from 50 years and above responded better to the active treatment with the PBASE system than other age groups. A significantly better effect in both FAS and PPAS was also obtained after two active treatments administered four weeks apart, as compared to one, when measured eight weeks following the first treatment.

Blockage/congestion of nose was the symptom most frequently reported as one of the five most significant problems in all treatment groups at all time-points. A significant effect of active treatment with the PBASE system on the N*asal congestion symptom score* was obtained four weeks after treatment (p=0.0056). An indication of better effect after two active treatments was also seen for the *Postnasal drip symptom score* eight weeks after first treatment (p=0.0271) and for the *Rhinorrhea symptom score* after 6 months (p= 0.0488).

Subjects seemed to have improved their PNIF value more after three months when the first treatment given was Placebo, as compared to subjects given two active treatments.

Based on descriptive analysis of SNOT-22 summary score, there were more subjects reporting any improvement after active treatment as compared to Placebo four weeks after treatment and after two active treatments as compared to one active treatment, eight weeks after first treatment.

A review of descriptive statistics for the EQ-5D-3L results also indicated a positive effect of active treatment on the domains *Pain/discomfort* and *Anxiety/Depression.* No effect was however seen on the EQ VAS.

A higher number of AEs occurred after treatment with Placebo as compared to the Low amplitude control and active treatment after the first treatment. During the period following the active treatment given to all subjects at Visit 3, more AEs occurred in the Placebo + Active group as compared to the two other groups (Low amplitude control + Active and Active + Active). A majority of AEs were assessed as not related to the investigational device or to clinical investigational procedures in all treatment groups. Anticipated AEs showed to be more frequently reported in relation to active treatment as compared to the Low amplitude control and Placebo with *Increased tear secretion*, *Increased nasal secretion* and *Slight discomfort* being the most frequently reported events. One SAE (stroke) assessed as not related to the investigational device or procedures occurred after the first treatment with the Low amplitude control.

To conclude, the present investigation demonstrated that the PBASE system was more efficacious than Placebo in reducing the weekly mean TVRSS in patients with idiopathic rhinitis. The statistical analyses showed significant differences between active treatment and Placebo regarding the primary efficacy /performance endpoint and for some of the secondary endpoints based on TVRSS. There were no concerns regarding safety in relation to treatment with the PBASE device in patients with idiopathic rhinitis.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Disposition of subjects

Table 14.1 Disposition of subjects by site, Safety analysis set

Site No.	Center	Active N=81	Low amplitude control N=47	Placebo N=79	Total N=207
001	Karolinska University Hospital	12 (14.8%)	16 (34.0%)	0	28 (13.5%)
002	Skåne University Hospital	26 (32.1%)	17 (36.2%)	26 (32.9%)	69 (33.3%)
003	Falu lasarett	10 (12.3%)	10 (21.3%)	0	20 (9.7%)
004	Västmanlands sjukhus Västerås	8 (9.9%)	0	18 (22.8%)	26 (12.6%)
005	Södermalms läkarhus	12 (14.8%)	4 (8.5%)	5 (6.3%)	21 (10.1%)
006	Liby&Rönndahl Läkarmottagning, Göteborg	13 (16.0%)	0	30 (38.0%)	43 (20.8%)

14.2 Demographics and other baseline characteristics

Table 14.2 Demographics, Safety analysis set (before and after first interim analysis)

		Old Active N=49	Low amplitude control N=47	New Active N=32	Placebo N=79	Total N=207
Age (years)	n/nmiss	49/0	47/0	32/0	79/0	207/0
	Mean (SD)	45.8 (12.2)	49.0 (10.0)	47.3 (11.8)	45.6 (13.6)	46.7 (12.2)
	Median (Min, Max)	46.0 (20, 65)	50.0 (25, 65)	48.5 (18, 64)	49.0 (18, 65)	49.0 (18, 65)
Gender	Male	21 (42.9%)	34 (72.3%)	15 (46.9%)	43 (54.4%)	113 (54.6%)
	Female	28 (57.1%)	13 (27.7%)	17 (53.1%)	36 (45.6%)	94 (45.4%)
Weight (kg)	n/nmiss	49/0	47/0	32/0	79/0	207/0
	Mean (SD)	74.6 (15.0)	80.7 (16.2)	81.2 (16.9)	77.9 (15.3)	78.3 (15.8)
	Median (Min, Max)	74.0 (50, 113)	79.0 (50, 114)	81.0 (50, 115)	79.0 (51, 115)	77.0 (50, 115)
Height (cm)	n/nmiss	49/0	47/0	32/0	79/0	207/0
	Mean (SD)	173.8 (10.0)	176.7 (8.1)	173.1 (10.0)	174.9 (9.5)	174.8 (9.4)
	Median (Min, Max)	173.0 (151, 195)	178.0 (156, 193)	174.0 (155, 198)	175.0 (155, 195)	175.0 (151, 198)

Table 14.3 Concurrent diseases, Safety analysis set

System Organ Class/Preferred Term*	Active N=81		Placebo N=79	
	n (%)	m	n (%)	m
Any medical history	62 (76.5%)	113	67 (84.8%)	125
Respiratory, thoracic and mediastinal disorders	50 (61.7%)	59	57 (72.2%)	64
Nasal inflammation	26 (32.1%)	26	21 (26.6%)	21
Nasal turbinate hypertrophy	11 (13.6%)	11	20 (25.3%)	20
Nasal congestion	9 (11.1%)	9	16 (20.3%)	16
Sleep apnoea syndrome	3 (3.7%)	3	1 (1.3%)	1
Asthma	2 (2.5%)	2	0	0
Asthma exercise induced	2 (2.5%)	2	0	0
Cough	1 (1.2%)	1	2 (2.5%)	2
Increased upper airway secretion	1 (1.2%)	1	1 (1.3%)	1
Mouth breathing	1 (1.2%)	1	0	0
Nasal septum deviation	1 (1.2%)	1	0	0
Nasal septum disorder	1 (1.2%)	1	0	0
Snoring	1 (1.2%)	1	0	0
Chronic obstructive pulmonary disease	0	0	1 (1.3%)	1
Dysphonia	0	0	1 (1.3%)	1
Laryngeal pain	0	0	1 (1.3%)	1
Endocrine disorders	5 (6.2%)	5	10 (12.7%)	10
Hypothyroidism	4 (4.9%)	4	10 (12.7%)	10
Goitre	1 (1.2%)	1	0	0
Vascular disorders	6 (7.4%)	6	10 (12.7%)	10
Hypertension	6 (7.4%)	6	9 (11.4%)	9
Raynaud's phenomenon	0	0	1 (1.3%)	1
Nervous system disorders	8 (9.9%)	9	5 (6.3%)	6
Migraine	5 (6.2%)	5	2 (2.5%)	2
Headache	2 (2.5%)	3	2 (2.5%)	2
Restless legs syndrome	1 (1.2%)	1	1 (1.3%)	1
Cervicobrachial syndrome	0	0	1 (1.3%)	1
Psychiatric disorders	6 (7.4%)	7	5 (6.3%)	5
Depression	2 (2.5%)	2	4 (5.1%)	4
Panic attack	2 (2.5%)	2	0	0
Menopausal depression	1 (1.2%)	1	0	0
Post-traumatic stress disorder	1 (1.2%)	1	1 (1.3%)	1
Sleep disorder	1 (1.2%)	1	0	0
Gastrointestinal disorders	4 (4.9%)	6	6 (7.6%)	6
Gastritis	1 (1.2%)	1	3 (3.8%)	3
Constipation	2 (2.5%)	2	0	0
Gastrooesophageal reflux disease	1 (1.2%)	1	2 (2.5%)	2
Flatulence	1 (1.2%)	1	0	0
Gastric ulcer	1 (1.2%)	1	0	0

System Organ Class/Preferred Term*	Active N=81 n (%)	Active N=81 m	Placebo N=79 n (%)	Placebo N=79 m
Inflammatory bowel disease	0	0	1 (1.3%)	1
Musculoskeletal and connective tissue disorders	4 (4.9%)	4	6 (7.6%)	6
Back pain	1 (1.2%)	1	2 (2.5%)	2
Osteoarthritis	1 (1.2%)	1	2 (2.5%)	2
Intervertebral disc protrusion	1 (1.2%)	1	0	0
Osteoporosis	1 (1.2%)	1	0	0
Arthropathy	0	0	1 (1.3%)	1
Fibromyalgia	0	0	1 (1.3%)	1
Metabolism and nutrition disorders	5 (6.2%)	5	1 (1.3%)	1
Hyperlipidaemia	2 (2.5%)	2	0	0
Vitamin B12 deficiency	2 (2.5%)	2	1 (1.3%)	1
Hypercholesterolaemia	1 (1.2%)	1	0	0
Reproductive system and breast disorders	1 (1.2%)	1	4 (5.1%)	4
Menopausal symptoms	1 (1.2%)	1	0	0
Atrophic vulvovaginitis	0	0	1 (1.3%)	1
Benign prostatic hyperplasia	0	0	1 (1.3%)	1
Erectile dysfunction	0	0	1 (1.3%)	1
Premenstrual syndrome	0	0	1 (1.3%)	1
Skin and subcutaneous tissue disorders	0	0	4 (5.1%)	4
Dermatitis	0	0	2 (2.5%)	2
Eczema	0	0	1 (1.3%)	1
Pruritus	0	0	1 (1.3%)	1
Infections and infestations	3 (3.7%)	3	2 (2.5%)	2
Nasopharyngitis	1 (1.2%)	1	2 (2.5%)	2
Borrelia infection	1 (1.2%)	1	0	0
Urinary tract infection	1 (1.2%)	1	0	0
Congenital, familial and genetic disorders	0	0	2 (2.5%)	2
Tourette's disorder	0	0	1 (1.3%)	1
Type IIa hyperlipidaemia	0	0	1 (1.3%)	1
Cardiac disorders	1 (1.2%)	1	1 (1.3%)	1
Cardiomyopathy	1 (1.2%)	1	0	0
Arrhythmia	0	0	1 (1.3%)	1
Ear and labyrinth disorders	1 (1.2%)	1	0	0
Meniere's disease	1 (1.2%)	1	0	0
Eye disorders	1 (1.2%)	1	1 (1.3%)	1
Blepharitis	1 (1.2%)	1	0	0
Cataract	0	0	1 (1.3%)	1
Immune system disorders	1 (1.2%)	1	0	0
Allergy to metals	1 (1.2%)	1	0	0
Injury, poisoning and procedural complications	1 (1.2%)	1	0	0
Face injury	1 (1.2%)	1	0	0

System Organ Class/Preferred Term*	Active N=81		Placebo N=79	
	n (%)	m	n (%)	m
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.2%)	1	0	0
Adenoma benign	1 (1.2%)	1	0	0
Social circumstances	1 (1.2%)	1	0	0
Menopause	1 (1.2%)	1	0	0
Surgical and medical procedures	1 (1.2%)	1	0	0
Continuous positive airway pressure	1 (1.2%)	1	0	0
General disorders and administration site conditions	0	0	1 (1.3%)	1
Pain	0	0	1 (1.3%)	1
Investigations	0	0	1 (1.3%)	1
Blood cholesterol increased	0	0	1 (1.3%)	1
Renal and urinary disorders	0	0	1 (1.3%)	1
Urinary incontinence	0	0	1 (1.3%)	1

n = number of patients, m = number of mentions, *Coded acc to MedDRA version 16.0E

Percentages are based on the number of subjects within each treatment group

Partially missing start and stop date were manually classified as medical history or concurrent disease

Table 14.4 Prior medications by ATC levels 2 and 5, Safety analysis set

ATC level 2 (Therapeutic main group)/ATC level5 (Chemical substance)	Active N=81		Placebo N=79	
	n (%)	m	n (%)	m
Any prior medication	9 (11.1%)	10	10 (12.7%)	16
ANALGESICS	3 (3.7%)	3	4 (5.1%)	6
paracetamol	3 (3.7%)	3	2 (2.5%)	2
acetylsalicylic acid, combinations excl. psycholeptics	0	0	2 (2.5%)	2
sumatriptan	0	0	1 (1.3%)	1
zolmitriptan	0	0	1 (1.3%)	1
NASAL PREPARATIONS	3 (3.7%)	3	4 (5.1%)	4
oxymetazoline	2 (2.5%)	2	2 (2.5%)	2
xylometazoline	0	0	2 (2.5%)	2
mometasone	1 (1.2%)	1	0	0
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	2 (2.5%)	2	3 (3.8%)	3
ibuprofen	1 (1.2%)	1	3 (3.8%)	3
diclofenac	1 (1.2%)	1	0	0
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	1 (1.2%)	1	0	0
papaverine	1 (1.2%)	1	0	0
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	1 (1.2%)	1	0	0
norethisterone and estrogen	1 (1.2%)	1	0	0
ANTIHISTAMINES FOR SYSTEMIC USE	0	0	1 (1.3%)	1
cetirizine	0	0	1 (1.3%)	1
COUGH AND COLD PREPARATIONS	0	0	1 (1.3%)	1
opium derivatives and expectorants	0	0	1 (1.3%)	1
DRUGS FOR ACID RELATED DISORDERS	0	0	1 (1.3%)	1
omeprazole	0	0	1 (1.3%)	1

n = number of patients, m = number of mentions

Percentages are based on the number of subjects within each treatment group

Medication with partially missing start and stop date were manually classified as concomitant or prior

Table 14.5 Concomitant medication by ATC levels 2 and 5, Safety analysis set

ATC level 2 (Therapeutic main group)/ATC level5 (Chemical substance)	Active N=81		Placebo N=79	
	n (%)	m	n (%)	m
Any concomitant medication	56 (69.1%)	190	67 (84.8%)	219
NASAL PREPARATIONS	35 (43.2%)	50	43 (54.4%)	66
mometasone	17 (21.0%)	17	19 (24.1%)	19
oxymetazoline	14 (17.3%)	15	18 (22.8%)	20
xylometazoline	10 (12.3%)	10	14 (17.7%)	15
phenylpropanolamine	3 (3.7%)	3	4 (5.1%)	5
budesonide	4 (4.9%)	4	3 (3.8%)	3
fluticasone	0	0	2 (2.5%)	2
ipratropium bromide	1 (1.2%)	1	1 (1.3%)	2
ANALGESICS	19 (23.5%)	30	19 (24.1%)	37
paracetamol	17 (21.0%)	25	17 (21.5%)	28
acetylsalicylic acid, combinations excl. psycholeptics	1 (1.2%)	1	3 (3.8%)	4
acetylsalicylic acid	0	0	1 (1.3%)	1
tramadol	2 (2.5%)	2	1 (1.3%)	1
sumatriptan	1 (1.2%)	1	2 (2.5%)	2
rizatriptan	1 (1.2%)	1	0	0
zolmitriptan	0	0	1 (1.3%)	1
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	13 (16.0%)	18	17 (21.5%)	30
ibuprofen	7 (8.6%)	9	9 (11.4%)	15
diclofenac	3 (3.7%)	3	4 (5.1%)	10
naproxen	3 (3.7%)	4	4 (5.1%)	4
etoricoxib	1 (1.2%)	1	0	0
glucosamine	1 (1.2%)	1	0	0
Other antiinflammatory and antirheumatic agents, non-steroids	0	0	1 (1.3%)	1
THYROID THERAPY	5 (6.2%)	6	9 (11.4%)	10
levothyroxine sodium	5 (6.2%)	6	8 (10.1%)	9
thyroid gland preparations	0	0	1 (1.3%)	1
PSYCHOANALEPTICS	7 (8.6%)	8	8 (10.1%)	8
citalopram	3 (3.7%)	3	0	0
sertraline	1 (1.2%)	1	3 (3.8%)	3
mirtazapine	2 (2.5%)	2	0	0
escitalopram	1 (1.2%)	1	2 (2.5%)	2
duloxetine	1 (1.2%)	1	1 (1.3%)	1
fluoxetine	0	0	1 (1.3%)	1
paroxetine	0	0	1 (1.3%)	1
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	7 (8.6%)	8	4 (5.1%)	4
estradiol	1 (1.2%)	1	2 (2.5%)	2
conjugated estrogens	1 (1.2%)	1	0	0
desogestrel	1 (1.2%)	1	0	0
drospirenone and ethinylestradiol	1 (1.2%)	1	0	0

ATC level 2 (Therapeutic main group)/ATC level5 (Chemical substance)	Active N=81		Placebo N=79	
	n (%)	m	n (%)	m
levonorgestrel	1 (1.2%)	1	0	0
levonorgestrel and ethinylestradiol	1 (1.2%)	1	0	0
norethisterone and estrogen	1 (1.2%)	1	0	0
norethisterone and ethinylestradiol	1 (1.2%)	1	0	0
norgestimate and ethinylestradiol	0	0	1 (1.3%)	1
tibolone	0	0	1 (1.3%)	1
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	6 (7.4%)	10	2 (2.5%)	2
terbutaline	4 (4.9%)	4	0	0
budesonide	2 (2.5%)	2	0	0
salbutamol	1 (1.2%)	2	0	0
Adrenergics and other drugs for obstructive airway diseases	1 (1.2%)	1	0	0
salmeterol and other drugs for obstructive airway diseases	1 (1.2%)	1	0	0
formoterol and other drugs for obstructive airway diseases	0	0	1 (1.3%)	1
indacaterol	0	0	1 (1.3%)	1
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	5 (6.2%)	6	6 (7.6%)	6
enalapril	1 (1.2%)	2	4 (5.1%)	4
losartan	2 (2.5%)	2	1 (1.3%)	1
candesartan and diuretics	1 (1.2%)	1	0	0
ramipril	1 (1.2%)	1	0	0
losartan and diuretics	0	0	1 (1.3%)	1
ANTIHISTAMINES FOR SYSTEMIC USE	2 (2.5%)	2	6 (7.6%)	6
cetirizine	0	0	3 (3.8%)	3
desloratadine	0	0	2 (2.5%)	2
ebastine	1 (1.2%)	1	1 (1.3%)	1
loratadine	1 (1.2%)	1	0	0
COUGH AND COLD PREPARATIONS	2 (2.5%)	4	5 (6.3%)	9
opium derivatives and expectorants	2 (2.5%)	3	3 (3.8%)	4
combinations	0	0	2 (2.5%)	2
acetylcysteine	1 (1.2%)	1	1 (1.3%)	1
bromhexine	0	0	1 (1.3%)	1
ethylmorphine	0	0	1 (1.3%)	1
DRUGS FOR ACID RELATED DISORDERS	4 (4.9%)	4	5 (6.3%)	8
omeprazole	4 (4.9%)	4	4 (5.1%)	6
calcium carbonate	0	0	1 (1.3%)	1
magnesium carbonate	0	0	1 (1.3%)	1
ANTIBACTERIALS FOR SYSTEMIC USE	5 (6.2%)	6	4 (5.1%)	5
nitrofurantoin	2 (2.5%)	2	0	0
phenoxymethylpenicillin	2 (2.5%)	2	0	0
doxycycline	1 (1.2%)	1	2 (2.5%)	2
cefadroxil	1 (1.2%)	1	0	0
flucloxacillin	0	0	1 (1.3%)	1

ATC level 2 (Therapeutic main group)/ATC level5 (Chemical substance)	Active N=81		Placebo N=79	
	n (%)	m	n (%)	m
lymecycline	0	0	1 (1.3%)	1
metronidazole	0	0	1 (1.3%)	1
BETA BLOCKING AGENTS	5 (6.2%)	6	2 (2.5%)	2
metoprolol	4 (4.9%)	5	2 (2.5%)	2
atenolol	1 (1.2%)	1	0	0
PSYCHOLEPTICS	4 (4.9%)	4	2 (2.5%)	2
propiomazine	3 (3.7%)	3	0	0
zolpidem	1 (1.2%)	1	0	0
aripiprazole	0	0	1 (1.3%)	1
hydroxyzine	0	0	1 (1.3%)	1
ANTIANEMIC PREPARATIONS	2 (2.5%)	2	3 (3.8%)	4
cyanocobalamin	1 (1.2%)	1	2 (2.5%)	2
Vitamin B12 (cyanocobalamin and analogues)	1 (1.2%)	1	1 (1.3%)	1
folic acid	0	0	1 (1.3%)	1
LIPID MODIFYING AGENTS	3 (3.7%)	3	3 (3.8%)	4
simvastatin	2 (2.5%)	2	1 (1.3%)	1
atorvastatin	0	0	2 (2.5%)	2
rosuvastatin	1 (1.2%)	1	0	0
ezetimibe	0	0	1 (1.3%)	1
ANTITHROMBOTIC AGENTS	3 (3.7%)	3	0	0
acetylsalicylic acid	3 (3.7%)	3	0	0
OTHER GYNECOLOGICALS	1 (1.2%)	1	3 (3.8%)	3
plastic IUD with progestogen	0	0	3 (3.8%)	3
bromocriptine	1 (1.2%)	1	0	0
UROLOGICALS	0	0	3 (3.8%)	3
alfuzosin	0	0	1 (1.3%)	1
fesoterodine	0	0	1 (1.3%)	1
tadalafil	0	0	1 (1.3%)	1
CORTICOSTEROIDS FOR SYSTEMIC USE	2 (2.5%)	5	1 (1.3%)	1
prednisolone	2 (2.5%)	5	0	0
methylprednisolone	0	0	1 (1.3%)	1
DIURETICS	2 (2.5%)	3	0	0
furosemide	1 (1.2%)	1	0	0
hydrochlorothiazide and potassium-sparing agents	1 (1.2%)	1	0	0
spironolactone	1 (1.2%)	1	0	0
DRUGS FOR CONSTIPATION	2 (2.5%)	2	0	0
ispaghula (psylla seeds)	1 (1.2%)	1	0	0
macrogol, combinations	1 (1.2%)	1	0	0
CALCIUM CHANNEL BLOCKERS	1 (1.2%)	1	2 (2.5%)	2
amlodipine	1 (1.2%)	1	1 (1.3%)	1
nifedipine	0	0	1 (1.3%)	1
OPHTHALMOLOGICALS	0	0	1 (1.3%)	2

ATC level 2 (Therapeutic main group)/ATC level5 (Chemical substance)	Active N=81		Placebo N=79	
	n (%)	m	n (%)	m
dexamethasone	0	0	1 (1.3%)	1
nepafenac	0	0	1 (1.3%)	1
ANTIEPILEPTICS	1 (1.2%)	1	0	0
pregabalin	1 (1.2%)	1	0	0
ANTIGOUT PREPARATIONS	1 (1.2%)	1	0	0
allopurinol	1 (1.2%)	1	0	0
ANTIHEMORRHAGICS	1 (1.2%)	1	0	0
tranexamic acid	1 (1.2%)	1	0	0
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	1 (1.2%)	1	0	0
silicones	1 (1.2%)	1	0	0
DRUGS FOR TREATMENT OF BONE DISEASES	1 (1.2%)	1	0	0
alendronic acid	1 (1.2%)	1	0	0
MINERAL SUPPLEMENTS	1 (1.2%)	1	0	0
Calcium, combinations with vitamin D and/or other drugs	1 (1.2%)	1	0	0
MUSCLE RELAXANTS	1 (1.2%)	1	0	0
chlorzoxazone	1 (1.2%)	1	0	0
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	1 (1.2%)	1	0	0
diclofenac	1 (1.2%)	1	0	0
ANTHELMINTICS	0	0	1 (1.3%)	1
pyrvinium	0	0	1 (1.3%)	1
ANTI-PARKINSON DRUGS	0	0	1 (1.3%)	1
pramipexole	0	0	1 (1.3%)	1
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	0	0	1 (1.3%)	1
mesalazine	0	0	1 (1.3%)	1
ANTIMYCOTICS FOR SYSTEMIC USE	0	0	1 (1.3%)	1
fluconazole	0	0	1 (1.3%)	1
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	0	0	1 (1.3%)	1
metronidazole	0	0	1 (1.3%)	1

n = number of patients, m = number of mentions

Percentages are based on the number of subjects within each treatment group

Medication with partially missing start and stop date were manually classified as concomitant or prior

14.3 Efficacy/performance data

14.3.1 Primary endpoint

Table 14.6 Summary of weekly mean TVRSS and change from baseline up to Week 4, PPAS

Week	Statistic	Active N=67	Placebo N=63
Week -1	n	67	63
	Mean (SD)	4.20 (1.62)	3.93 (1.42)
	95% CI	(3.80, 4.59)	(3.57, 4.29)
	Median	4.00	4.00
	Q1, Q3	3.00, 5.67	2.57, 4.86
	Min, Max	1.7, 8.7	1.8, 7.7
Week 1	n	67	63
	Mean (SD)	3.83 (1.72)	3.98 (1.75)
	95% CI	(3.41, 4.25)	(3.54, 4.42)
	Median	3.50	3.50
	Q1, Q3	2.43, 5.00	2.71, 4.86
	Min, Max	1.1, 9.3	1.7, 9.0
Week 2	n	67	63
	Mean (SD)	3.51 (1.88)	3.91 (1.83)
	95% CI	(3.05, 3.97)	(3.45, 4.37)
	Median	3.14	3.67
	Q1, Q3	2.00, 4.67	2.43, 4.86
	Min, Max	0.5, 10.0	1.1, 9.6
Change from baseline, Week 2	n	67	63
	Mean (SD)	-0.69 (1.60)	-0.02 (1.26)
	95% CI	(-1.08, -0.30)	(-0.34, 0.30)
	Median	-0.57	-0.03
	Q1, Q3	-1.48, 0.17	-0.71, 0.55
	Min, Max	-4.5, 4.0	-3.6, 4.5
Week 3	n	67	63
	Mean (SD)	3.49 (1.80)	3.64 (1.72)
	95% CI	(3.05, 3.93)	(3.21, 4.07)
	Median	3.14	3.20
	Q1, Q3	2.17, 4.86	2.57, 4.83
	Min, Max	0.9, 9.0	0.9, 8.2
Change from baseline, Week 3	n	67	63
	Mean (SD)	-0.71 (1.63)	-0.29 (1.37)
	95% CI	(-1.10, -0.31)	(-0.64, 0.05)
	Median	-0.80	-0.33
	Q1, Q3	-1.54, 0.20	-1.25, 0.55
	Min, Max	-5.1, 5.0	-3.9, 2.7
Week 4	n	67	63
	Mean (SD)	3.39 (1.61)	3.71 (1.88)
	95% CI	(2.99, 3.78)	(3.23, 4.18)
	Median	3.00	3.50
	Q1, Q3	2.17, 4.43	2.43, 4.80

Week	Statistic	Active N=67	Placebo N=63
	Min, Max	0.6, 8.6	0.5, 10.8
Change from baseline, Week 4	n	67	63
	Mean (SD)	-0.81 (1.41)	-0.23 (1.43)
	95% CI	(-1.15, -0.47)	(-0.59, 0.14)
	Median	-0.67	-0.17
	Q1, Q3	-1.57, 0.00	-1.00, 0.50
	Min, Max	-4.7, 2.5	-3.9, 4.1

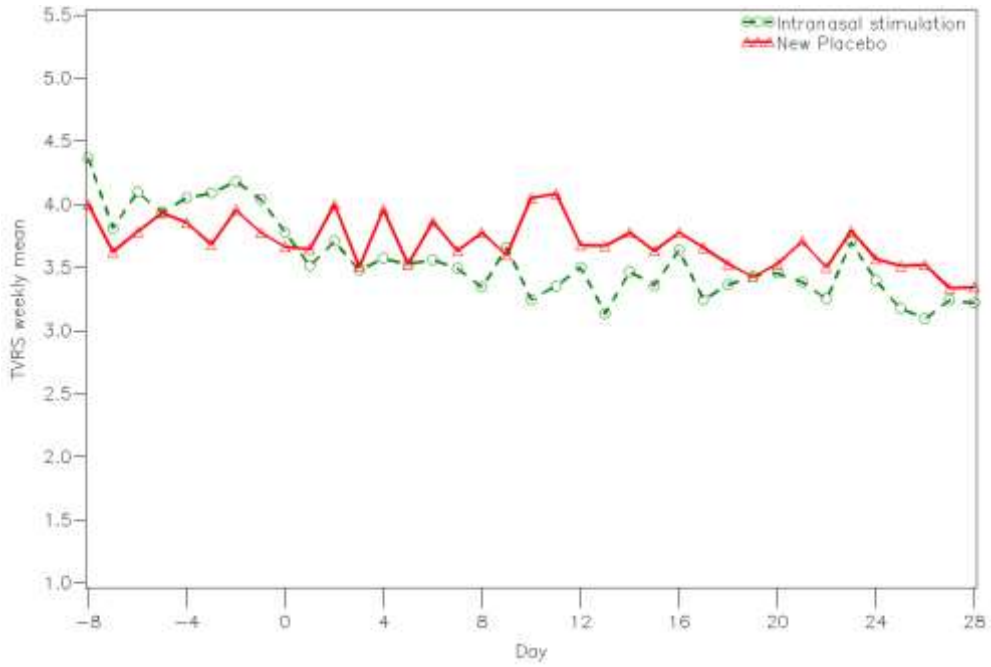


Figure 14.1 TVRSS mean by treatment and day up to Week 4, FAS

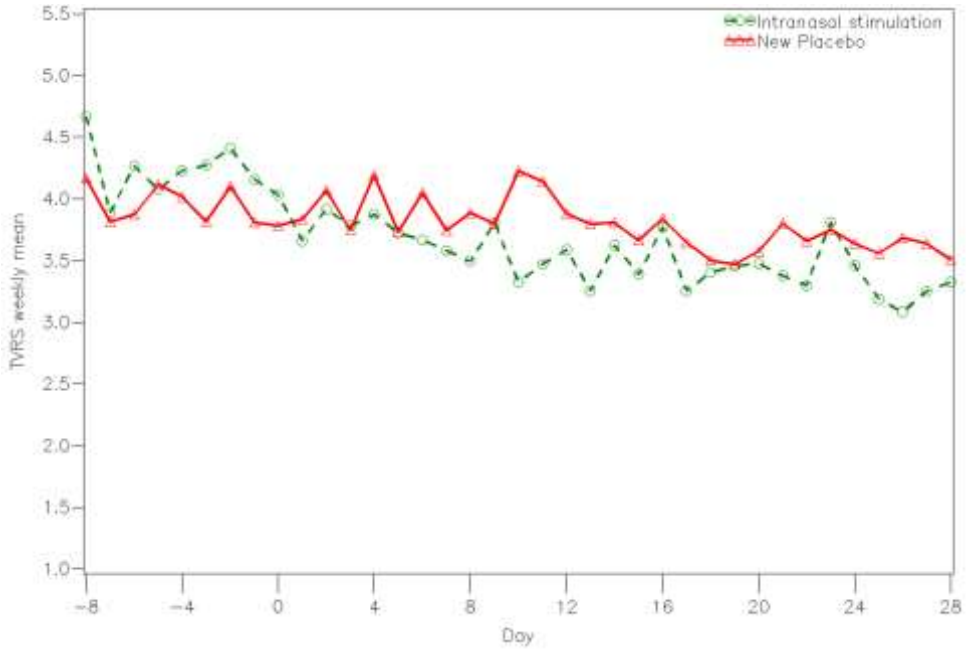


Figure 14.2 TVRSS mean by treatment and day up to Week 4, PPAS

Table 14.7 Summary of weekly mean TVRSS and change from baseline up to Week 4, FAS (before and after first interim analysis)

Week	Statistic	Old Active N=49	Low amplitude control N=47	New Active N=32	Placebo N=79
Week -1	N	49	47	32	79
	Mean (SD)	3.92 (1.67)	4.11 (1.63)	4.21 (1.61)	3.80 (1.40)
	95% CI	(3.44, 4.40)	(3.64, 4.59)	(3.63, 4.79)	(3.49, 4.11)
	Median	3.71	3.86	4.00	3.43
	Q1, Q3	2.57, 4.57	3.00, 5.50	3.00, 5.17	2.50, 4.75
	Min, Max	1.2, 8.7	1.3, 7.5	2.0, 7.7	1.5, 7.7
Week 1	n	49	47	32	79
	Mean (SD)	3.58 (1.73)	3.57 (1.74)	3.68 (1.71)	3.79 (1.68)
	95% CI	(3.09, 4.08)	(3.06, 4.08)	(3.06, 4.29)	(3.41, 4.16)
	Median	3.29	3.40	3.61	3.50
	Q1, Q3	2.33, 4.29	2.14, 4.43	2.36, 5.00	2.67, 4.71
	Min, Max	1.0, 9.3	1.0, 7.5	0.9, 8.3	1.3, 9.0
Week 2	n	49	46	32	79
	Mean (SD)	3.33 (1.85)	3.64 (1.64)	3.54 (1.76)	3.77 (1.78)
	95% CI	(2.79, 3.86)	(3.15, 4.12)	(2.90, 4.17)	(3.37, 4.17)
	Median	2.83	3.29	3.50	3.50
	Q1, Q3	2.00, 4.33	2.43, 4.71	2.29, 4.36	2.33, 4.71
	Min, Max	1.0, 10.0	1.1, 7.6	0.5, 7.4	0.4, 9.6
Change from baseline, Week 2	n	49	46	32	79
	Mean (SD)	-0.59 (1.59)	-0.50 (1.13)	-0.67 (1.47)	-0.03 (1.35)
	95% CI	(-1.05, -0.14)	(-0.84, -0.16)	(-1.20, -0.14)	(-0.33, 0.27)
	Median	-0.38	-0.44	-0.50	-0.07
	Q1, Q3	-1.14, 0.19	-1.14, 0.33	-1.51, 0.30	-0.79, 0.55

Week	Statistic	Old Active N=49	Low amplitude control N=47	New Active N=32	Placebo N=79
	Min, Max	-4.5, 4.0	-3.6, 2.1	-4.2, 2.6	-3.6, 4.5
Week 3	n	48	45	32	79
	Mean (SD)	3.28 (1.82)	3.31 (1.78)	3.68 (1.77)	3.65 (1.81)
	95% CI	(2.75, 3.80)	(2.78, 3.84)	(3.04, 4.32)	(3.24, 4.06)
	Median	2.77	2.80	3.70	3.20
	Q1, Q3	2.00, 3.83	2.00, 4.43	2.21, 5.07	2.57, 4.71
	Min, Max	0.9, 9.0	0.9, 7.4	0.3, 7.3	0.9, 8.8
Change from baseline, Week 3	n	48	45	32	79
	Mean (SD)	-0.58 (1.71)	-0.82 (1.56)	-0.53 (1.64)	-0.15 (1.58)
	95% CI	(-1.08, -0.08)	(-1.28, -0.35)	(-1.12, 0.06)	(-0.50, 0.20)
	Median	-0.65	-0.71	-0.25	-0.36
	Q1, Q3	-1.63, 0.35	-1.57, 0.14	-1.38, 0.61	-1.25, 0.57
	Min, Max	-5.0, 5.0	-4.7, 3.2	-5.1, 2.3	-3.9, 4.6
Week 4	n	46	45	32	79
	Mean (SD)	3.17 (1.61)	3.16 (1.63)	3.59 (1.53)	3.61 (1.82)
	95% CI	(2.69, 3.64)	(2.67, 3.65)	(3.04, 4.14)	(3.20, 4.02)
	Median	2.93	2.67	3.35	3.43
	Q1, Q3	2.14, 4.00	2.00, 4.00	2.75, 4.71	2.33, 4.67
	Min, Max	0.6, 8.6	0.5, 7.1	0.1, 6.3	0.5, 10.8
Change from baseline, Week 4	n	46	45	32	79
	Mean (SD)	-0.72 (1.50)	-0.97 (1.51)	-0.62 (1.31)	-0.19 (1.44)
	95% CI	(-1.16, -0.27)	(-1.42, -0.51)	(-1.10, -0.15)	(-0.51, 0.13)
	Median	-0.63	-0.75	-0.46	-0.29
	Q1, Q3	-1.57, 0.14	-1.71, 0.00	-1.26, 0.17	-1.10, 0.50
	Min, Max	-4.7, 2.5	-5.2, 2.2	-4.7, 2.3	-3.9, 4.1

Table 14.8 Summary of weekly mean TVRSS and change from baseline up to Week 4, PPAS (before and after first interim analysis)

Week	Statistic	Old Active N=40	Low amplitude control N=40	New Active N=27	Placebo N=63
Week -1	n	40	40	27	63
	Mean (SD)	4.10 (1.62)	4.35 (1.57)	4.35 (1.64)	3.93 (1.42)
	95% CI	(3.58, 4.61)	(3.84, 4.85)	(3.70, 5.00)	(3.57, 4.29)
	Median	4.00	4.10	4.00	4.00
	Q1, Q3	2.92, 5.33	3.10, 5.58	3.00, 5.67	2.57, 4.86
	Min, Max	1.7, 8.7	1.8, 7.5	2.0, 7.7	1.8, 7.7
Week 1	n	40	40	27	63
	Mean (SD)	3.81 (1.74)	3.73 (1.81)	3.87 (1.73)	3.98 (1.75)
	95% CI	(3.25, 4.36)	(3.15, 4.31)	(3.19, 4.56)	(3.54, 4.42)
	Median	3.43	3.69	3.86	3.50
	Q1, Q3	2.42, 4.48	2.14, 4.69	2.43, 5.00	2.71, 4.86
	Min, Max	1.4, 9.3	1.0, 7.5	1.1, 8.3	1.7, 9.0
Week 2	n	40	40	27	63
	Mean (SD)	3.34 (1.95)	3.77 (1.65)	3.76 (1.78)	3.91 (1.83)
	95% CI	(2.71, 3.96)	(3.24, 4.30)	(3.06, 4.46)	(3.45, 4.37)
	Median	2.71	3.71	3.86	3.67
	Q1, Q3	1.93, 4.40	2.43, 4.93	2.57, 4.67	2.43, 4.86
	Min, Max	1.1, 10.0	1.1, 7.6	0.5, 7.4	1.1, 9.6
Change from baseline, Week 2	n	40	40	27	63
	Mean (SD)	-0.76 (1.64)	-0.57 (1.16)	-0.59 (1.56)	-0.02 (1.26)
	95% CI	(-1.28, -0.23)	(-0.94, -0.20)	(-1.21, 0.03)	(-0.34, 0.30)
	Median	-0.57	-0.64	-0.43	-0.03
	Q1, Q3	-1.42, -0.01	-1.14, 0.32	-1.60, 0.43	-0.71, 0.55
	Min, Max	-4.5, 4.0	-3.6, 2.1	-4.2, 2.6	-3.6, 4.5
Week 3	n	40	40	27	63
	Mean (SD)	3.21 (1.80)	3.44 (1.82)	3.91 (1.73)	3.64 (1.72)
	95% CI	(2.63, 3.79)	(2.85, 4.02)	(3.22, 4.59)	(3.21, 4.07)
	Median	2.59	2.83	4.00	3.20
	Q1, Q3	2.00, 3.79	2.00, 4.79	2.57, 5.43	2.57, 4.83
	Min, Max	0.9, 9.0	0.9, 7.4	1.0, 7.3	0.9, 8.2
Change from baseline, Week 3	n	40	40	27	63
	Mean (SD)	-0.88 (1.57)	-0.91 (1.60)	-0.44 (1.72)	-0.29 (1.37)
	95% CI	(-1.39, -0.38)	(-1.42, -0.40)	(-1.12, 0.23)	(-0.64, 0.05)
	Median	-0.92	-0.86	-0.21	-0.33
	Q1, Q3	-1.89, -0.19	-1.62, -0.11	-1.38, 0.77	-1.25, 0.55
	Min, Max	-5.0, 5.0	-4.7, 3.2	-5.1, 2.3	-3.9, 2.7
Week 4	n	40	40	27	63
	Mean (SD)	3.17 (1.68)	3.28 (1.69)	3.71 (1.49)	3.71 (1.88)
	95% CI	(2.64, 3.71)	(2.74, 3.82)	(3.12, 4.29)	(3.23, 4.18)
	Median	2.86	2.86	3.50	3.50
	Q1, Q3	2.14, 4.00	2.07, 4.46	3.00, 5.00	2.43, 4.80
	Min, Max	0.6, 8.6	0.5, 7.1	1.0, 6.3	0.5, 10.8
Change from baseline, Week 4	n	40	40	27	63
	Mean (SD)	-0.92 (1.46)	-1.07 (1.51)	-0.65 (1.33)	-0.23 (1.43)

Week	Statistic	Old Active N=40	Low amplitude control N=40	New Active N=27	Placebo N=63
	95% CI	(-1.39, -0.45)	(-1.55, -0.58)	(-1.17, -0.12)	(-0.59, 0.14)
	Median	-0.83	-0.89	-0.51	-0.17
	Q1, Q3	-1.64, -0.05	-1.82, -0.17	-1.14, 0.00	-1.00, 0.50
	Min, Max	-4.7, 2.5	-5.2, 2.2	-4.7, 2.3	-3.9, 4.1

Table 14.9 Summary of weekly mean TVRSS and change from baseline in males up to Week 4, FAS

Week	Statistic	Active N=81	Placebo N=79
Week -1	n	36	43
	Mean (SD)	3.95 (1.63)	3.49 (1.21)
	95% CI	(3.40, 4.50)	(3.12, 3.87)
	Median	4.00	3.17
	Q1, Q3	2.62, 5.00	2.50, 4.43
	Min, Max	1.2, 7.7	1.5, 6.1
Week 1	n	36	43
	Mean (SD)	3.57 (1.84)	3.41 (1.45)
	95% CI	(2.95, 4.20)	(2.96, 3.85)
	Median	3.46	3.29
	Q1, Q3	2.36, 4.23	2.14, 4.20
	Min, Max	0.9, 9.3	1.4, 8.6
Week 2	n	36	43
	Mean (SD)	3.40 (1.60)	3.48 (1.63)
	95% CI	(2.86, 3.94)	(2.98, 3.98)
	Median	3.17	3.14
	Q1, Q3	2.21, 4.07	2.29, 4.43
	Min, Max	0.7, 7.4	1.1, 9.6
Change from baseline, Week 2	n	36	43
	Mean (SD)	-0.55 (1.59)	-0.01 (1.40)
	95% CI	(-1.09, -0.02)	(-0.44, 0.42)
	Median	-0.37	-0.19
	Q1, Q3	-1.11, 0.08	-0.79, 0.43
	Min, Max	-4.5, 3.0	-3.6, 4.5
Week 3	n	36	43
	Mean (SD)	3.38 (1.59)	3.25 (1.56)
	95% CI	(2.84, 3.92)	(2.77, 3.73)
	Median	3.23	2.86
	Q1, Q3	2.31, 4.24	2.29, 4.00
	Min, Max	0.3, 7.3	0.9, 7.8
Change from baseline, Week 3	n	36	43
	Mean (SD)	-0.57 (1.43)	-0.24 (1.52)
	95% CI	(-1.06, -0.09)	(-0.71, 0.23)
	Median	-0.37	-0.40
	Q1, Q3	-0.99, 0.35	-1.00, 0.29
	Min, Max	-5.1, 1.4	-3.9, 4.6
Week 4	n	36	43

Week	Statistic	Active N=81	Placebo N=79
	Mean (SD)	3.37 (1.39)	3.20 (1.27)
	95% CI	(2.90, 3.84)	(2.81, 3.60)
	Median	3.18	3.00
	Q1, Q3	2.38, 4.36	2.00, 4.14
	Min, Max	0.1, 5.9	0.8, 5.7
Change from baseline, Week 4	n	36	43
	Mean (SD)	-0.58 (1.30)	-0.29 (1.25)
	95% CI	(-1.02, -0.14)	(-0.67, 0.10)
	Median	-0.58	-0.36
	Q1, Q3	-1.18, 0.39	-1.00, 0.43
	Min, Max	-4.7, 1.7	-3.9, 3.3

Table 14.10 ANCOVA analysis of change from baseline in weekly mean TVRSS in males at Week 4, FAS

		Estimate		Difference to Placebo		
Treatment	n	LS mean	95% CI	LS mean	95% CI	P-value
Active	36	-0.465	-0.832, -0.098	-0.079	-0.579, 0.422	0.7552
Placebo	43	-0.386	-0.722, -0.051			

Table 14.11 Summary of weekly mean TVRSS and change from baseline in females up to Week 4, FAS

Week	Statistic	Active N=81	Placebo N=79
Week -1	n	45	36
	Mean (SD)	4.10 (1.67)	4.17 (1.53)
	95% CI	(3.60, 4.60)	(3.65, 4.68)
	Median	4.00	4.08
	Q1, Q3	2.67, 5.17	2.75, 5.33
	Min, Max	1.7, 8.7	2.2, 7.7
Week 1	n	45	36
	Mean (SD)	3.66 (1.62)	4.24 (1.84)
	95% CI	(3.17, 4.14)	(3.62, 4.86)
	Median	3.29	3.70
	Q1, Q3	2.33, 5.00	2.86, 5.79
	Min, Max	1.1, 7.1	1.3, 9.0
Week 2	n	45	36
	Mean (SD)	3.42 (1.98)	4.11 (1.91)
	95% CI	(2.82, 4.01)	(3.47, 4.76)
	Median	2.86	3.69
	Q1, Q3	1.86, 4.60	2.73, 5.73
	Min, Max	0.5, 10.0	0.4, 9.3
Change from baseline, Week 2	n	45	36
	Mean (SD)	-0.68 (1.50)	-0.05 (1.30)
	95% CI	(-1.13, -0.23)	(-0.49, 0.39)

Week	Statistic	Active N=81	Placebo N=79
	Median	-0.57	0.29
	Q1, Q3	-1.57, 0.20	-0.96, 0.82
	Min, Max	-4.4, 4.0	-3.6, 2.2
Week 3	n	44	36
	Mean (SD)	3.49 (1.97)	4.13 (1.99)
	95% CI	(2.89, 4.09)	(3.45, 4.80)
	Median	3.14	3.76
	Q1, Q3	2.00, 5.07	2.79, 5.37
	Min, Max	0.9, 9.0	1.0, 8.8
Change from baseline, Week 3	n	44	36
	Mean (SD)	-0.55 (1.86)	-0.04 (1.66)
	95% CI	(-1.11, 0.02)	(-0.60, 0.52)
	Median	-0.95	-0.14
	Q1, Q3	-1.76, 0.61	-1.42, 0.77
	Min, Max	-5.0, 5.0	-2.7, 4.4
Week 4	n	42	36
	Mean (SD)	3.31 (1.74)	4.10 (2.23)
	95% CI	(2.77, 3.86)	(3.34, 4.85)
	Median	3.08	3.83
	Q1, Q3	2.00, 4.14	2.69, 5.20
	Min, Max	0.6, 8.6	0.5, 10.8
Change from baseline, Week 4	n	42	36
	Mean (SD)	-0.76 (1.52)	-0.07 (1.64)
	95% CI	(-1.24, -0.29)	(-0.63, 0.48)
	Median	-0.53	0.00
	Q1, Q3	-1.57, 0.00	-1.47, 0.60
	Min, Max	-4.7, 2.5	-3.0, 4.1

Table 14.12 ANCOVA analysis of change from baseline in weekly mean TVRSS in females at Week 4, FAS

		Estimate		Difference to Placebo		
Treatment	n	LS mean	95% CI	LS mean	95% CI	P-value
Active	42	-0.771	-1.247, -0.295	-0.710	-1.411, -0.009	0.0471
Placebo	36	-0.061	-0.575, 0.453			

Table 14.13 Summary of weekly mean TVRSS and change from baseline in non-allergic rhinitis patients up to Week 4, FAS

Week	Statistic	Active N=81	Placebo N=79
Week -1	n	63	60
	Mean (SD)	3.99 (1.76)	3.93 (1.43)
	95% CI	(3.55, 4.43)	(3.56, 4.30)
	Median	3.71	3.90
	Q1, Q3	2.57, 5.17	2.67, 4.85
	Min, Max	1.2, 8.7	1.5, 7.7
Week 1	n	63	60
	Mean (SD)	3.60 (1.84)	4.04 (1.60)
	95% CI	(3.14, 4.07)	(3.63, 4.45)
	Median	3.43	3.69
	Q1, Q3	2.14, 4.57	2.86, 4.83
	Min, Max	0.9, 9.3	1.4, 9.0
Week 2	n	63	60
	Mean (SD)	3.50 (1.90)	4.07 (1.58)
	95% CI	(3.03, 3.98)	(3.66, 4.48)
	Median	3.17	3.71
	Q1, Q3	2.00, 4.14	3.00, 4.86
	Min, Max	0.5, 10.0	1.5, 9.3
Change from baseline, Week 2	n	63	60
	Mean (SD)	-0.48 (1.58)	0.14 (1.21)
	95% CI	(-0.88, -0.09)	(-0.18, 0.45)
	Median	-0.33	0.13
	Q1, Q3	-1.14, 0.20	-0.51, 0.82
	Min, Max	-4.5, 4.0	-3.6, 3.3
Week 3	n	62	60
	Mean (SD)	3.44 (1.72)	3.98 (1.75)
	95% CI	(3.00, 3.87)	(3.53, 4.43)
	Median	3.23	3.64
	Q1, Q3	2.17, 4.86	2.79, 4.93
	Min, Max	0.3, 7.3	1.1, 8.8
Change from baseline, Week 3	n	62	60
	Mean (SD)	-0.50 (1.41)	0.05 (1.61)
	95% CI	(-0.86, -0.15)	(-0.36, 0.47)
	Median	-0.31	-0.18
	Q1, Q3	-1.21, 0.71	-1.13, 0.75
	Min, Max	-5.1, 2.3	-2.7, 4.6
Week 4	n	62	60
	Mean (SD)	3.40 (1.66)	3.95 (1.81)
	95% CI	(2.98, 3.82)	(3.48, 4.42)
	Median	3.17	3.77
	Q1, Q3	2.17, 4.67	2.63, 4.82
	Min, Max	0.1, 8.6	0.5, 10.8
Change from baseline, Week 4	n	62	60

Week	Statistic	Active N=81	Placebo N=79
	Mean (SD)	-0.54 (1.40)	0.02 (1.41)
	95% CI	(-0.90, -0.19)	(-0.34, 0.39)
	Median	-0.40	-0.06
	Q1, Q3	-1.25, 0.34	-1.00, 0.64
	Min, Max	-4.7, 2.5	-2.6, 4.1

Table 14.14 ANCOVA analysis of change from baseline in weekly mean TVRSS in non-allergic rhinitis patients at Week 4, FAS

		Estimate		Difference to Placebo		
Treatment	n	LS mean	95% CI	LS mean	95% CI	P-value
Active	62	-0.542	-0.876, -0.208	-0.561	-1.038, -0.085	0.0213
Placebo	60	0.020	-0.320, 0.359			

Table 14.15 Summary of weekly mean TVRS and change from baseline in rhinitis medicamentosa patients up to Week 4, FAS

Week	Statistic	Active N=81	Placebo N=79
Week -1	n	11	16
	Mean (SD)	3.61 (0.91)	3.36 (1.13)
	95% CI	(3.00, 4.22)	(2.76, 3.97)
	Median	3.57	2.87
	Q1, Q3	3.00, 4.00	2.43, 4.44
	Min, Max	2.4, 5.7	2.2, 5.3
Week 1	n	11	16
	Mean (SD)	3.27 (1.15)	2.95 (1.77)
	95% CI	(2.49, 4.04)	(2.01, 3.90)
	Median	3.00	2.76
	Q1, Q3	2.33, 4.14	1.76, 3.29
	Min, Max	1.7, 5.4	1.3, 8.6
Week 2	n	11	16
	Mean (SD)	2.76 (1.17)	2.67 (2.05)
	95% CI	(1.97, 3.55)	(1.57, 3.76)
	Median	2.86	2.29
	Q1, Q3	1.80, 4.29	1.86, 2.67
	Min, Max	1.3, 4.4	0.4, 9.6
Change from baseline, Week 2	n	11	16
	Mean (SD)	-0.85 (0.84)	-0.70 (1.73)
	95% CI	(-1.41, -0.29)	(-1.62, 0.23)
	Median	-0.93	-0.82
	Q1, Q3	-1.48, 0.00	-1.78, -0.02
	Min, Max	-2.1, 0.4	-3.6, 4.5
Week 3	n	11	16
	Mean (SD)	3.15 (1.74)	2.47 (1.55)
	95% CI	(1.98, 4.31)	(1.64, 3.29)

Week	Statistic	Active N=81	Placebo N=79
	Median	3.00	2.27
	Q1, Q3	1.71, 4.29	1.60, 2.86
	Min, Max	1.0, 7.0	0.9, 7.5
Change from baseline, Week 3	n	11	16
	Mean (SD)	-0.46 (1.90)	-0.90 (1.40)
	95% CI	(-1.74, 0.81)	(-1.64, -0.15)
	Median	-0.57	-0.79
	Q1, Q3	-1.80, 0.00	-1.69, -0.14
	Min, Max	-2.3, 4.6	-3.9, 2.4
Week 4	n	9	16
	Mean (SD)	3.01 (1.40)	2.39 (1.33)
	95% CI	(1.94, 4.09)	(1.68, 3.10)
	Median	3.00	1.86
	Q1, Q3	2.43, 4.00	1.50, 3.17
	Min, Max	0.6, 5.0	0.8, 5.6
Change from baseline, Week 4	n	9	16
	Mean (SD)	-0.69 (1.14)	-0.98 (1.43)
	95% CI	(-1.56, 0.19)	(-1.74, -0.21)
	Median	-0.67	-0.74
	Q1, Q3	-1.57, 0.33	-1.85, 0.02
	Min, Max	-2.8, 0.5	-3.9, 1.6

Table 14.16 ANCOVA analysis of change from baseline in weekly mean TVRSS in rhinitis medicamentosa patients at Week 4, FAS

		Estimate		Difference to Placebo		
Treatment	n	LS mean	95% CI	LS mean	95% CI	P-value
Active	9	-0.583	-1.466, 0.300	0.450	-0.659, 1.558	0.4091
Placebo	16	-1.033	-1.693, -0.373			

Table 14.17 Summary of weekly mean TVRS and change from baseline in combination patients up to Week 4, FAS

Week	Statistic	Active N=81	Placebo N=79
Week -1	n	7	3
	Mean (SD)	5.13 (0.87)	3.52 (1.99)
	95% CI	(4.33, 5.94)	(-1.43, 8.46)
	Median	5.00	3.00
	Q1, Q3	4.43, 5.83	1.83, 5.71
	Min, Max	4.0, 6.4	1.8, 5.7
Week 1	n	7	3
	Mean (SD)	4.34 (0.89)	3.19 (1.58)
	95% CI	(3.52, 5.16)	(-0.73, 7.12)
	Median	4.29	3.00
	Q1, Q3	3.57, 5.33	1.71, 4.86
	Min, Max	3.3, 5.6	1.7, 4.9
Week 2	n	7	3
	Mean (SD)	3.59 (1.82)	3.64 (2.31)
	95% CI	(1.90, 5.27)	(-2.10, 9.38)
	Median	4.67	3.00
	Q1, Q3	1.71, 5.00	1.71, 6.20
	Min, Max	1.4, 5.6	1.7, 6.2
Change from baseline, Week 2	n	7	3
	Mean (SD)	-1.55 (1.79)	0.12 (0.32)
	95% CI	(-3.21, 0.11)	(-0.67, 0.92)
	Median	-1.00	0.00
	Q1, Q3	-3.00, -0.14	-0.12, 0.49
	Min, Max	-4.1, 1.0	-0.1, 0.5
Week 3	n	7	3
	Mean (SD)	3.93 (2.69)	3.33 (2.23)
	95% CI	(1.44, 6.42)	(-2.21, 8.88)
	Median	3.40	3.00
	Q1, Q3	2.00, 5.50	1.29, 5.71
	Min, Max	0.9, 9.0	1.3, 5.7
Change from baseline, Week 3	n	7	3
	Mean (SD)	-1.20 (3.16)	-0.18 (0.32)
	95% CI	(-4.13, 1.72)	(-0.97, 0.60)
	Median	-2.27	0.00
	Q1, Q3	-2.43, 0.50	-0.55, 0.00
	Min, Max	-5.0, 5.0	-0.5, 0.0
Week 4	n	7	3
	Mean (SD)	3.26 (1.12)	3.31 (1.81)
	95% CI	(2.22, 4.29)	(-1.19, 7.80)
	Median	3.17	3.00
	Q1, Q3	2.86, 4.20	1.67, 5.25
	Min, Max	1.1, 4.4	1.7, 5.3
Change from baseline, Week 4	n	7	3
	Mean (SD)	-1.88 (1.54)	-0.21 (0.24)
	95% CI	(-3.30, -0.45)	(-0.79, 0.37)

Week	Statistic	Active N=81	Placebo N=79
	Median	-1.57	-0.17
	Q1, Q3	-2.67, -0.57	-0.46, 0.00
	Min, Max	-4.7, 0.0	-0.5, 0.0

Table 14.18 ANCOVA analysis of change from baseline in weekly mean TVRSS in combination patients at Week 4, FAS

		Estimate		Difference to Placebo		
Treatment	n	LS mean	95% CI	LS mean	95% CI	P-value
Active	7	-1.629	-2.825, -0.433	-0.842	-3.304, 1.620	0.4453
Placebo	3	-0.787	-2.750, 1.176			

Table 14.19 Summary of weekly mean TVRSS and change from baseline in age group 18-<35 up to Week 4, FAS

Week	Statistic	Active N=81	Placebo N=79
Week -1	n	13	18
	Mean (SD)	3.90 (1.36)	3.85 (1.35)
	95% CI	(3.07, 4.72)	(3.18, 4.53)
	Median	4.00	4.00
	Q1, Q3	3.00, 4.29	2.33, 5.14
	Min, Max	1.7, 6.5	1.8, 5.8
Week 1	n	13	18
	Mean (SD)	3.96 (2.00)	4.03 (2.16)
	95% CI	(2.75, 5.17)	(2.95, 5.10)
	Median	3.43	3.57
	Q1, Q3	3.17, 4.29	2.29, 5.00
	Min, Max	1.4, 9.3	1.3, 8.6
Week 2	n	13	18
	Mean (SD)	3.89 (1.52)	3.95 (2.28)
	95% CI	(2.97, 4.81)	(2.81, 5.08)
	Median	4.00	3.62
	Q1, Q3	3.14, 4.67	2.25, 4.86
	Min, Max	1.3, 6.3	0.4, 9.6
Change from baseline, Week 2	n	13	18
	Mean (SD)	-0.00 (1.50)	0.09 (1.77)
	95% CI	(-0.91, 0.90)	(-0.79, 0.98)
	Median	0.19	-0.06
	Q1, Q3	-0.98, 0.64	-0.71, 0.74
	Min, Max	-2.7, 3.0	-3.6, 4.5
Week 3	n	13	18
	Mean (SD)	3.81 (2.12)	4.00 (2.38)
	95% CI	(2.53, 5.09)	(2.81, 5.18)
	Median	3.17	3.24
	Q1, Q3	2.33, 5.33	2.25, 5.57

Week	Statistic	Active N=81	Placebo N=79
	Min, Max	1.2, 9.0	1.0, 8.2
Change from baseline, Week 3	n	13	18
	Mean (SD)	-0.09 (2.03)	0.14 (1.85)
	95% CI	(-1.31, 1.14)	(-0.78, 1.06)
	Median	-0.81	-0.29
	Q1, Q3	-1.71, 0.67	-1.08, 0.91
	Min, Max	-2.1, 5.0	-2.4, 4.6
Week 4	n	13	18
	Mean (SD)	3.33 (1.94)	3.64 (2.13)
	95% CI	(2.16, 4.51)	(2.58, 4.69)
	Median	3.17	3.71
	Q1, Q3	2.14, 4.00	1.71, 4.80
	Min, Max	1.4, 8.6	0.5, 8.0
Change from baseline, Week 4	n	13	18
	Mean (SD)	-0.56 (1.24)	-0.22 (1.37)
	95% CI	(-1.31, 0.19)	(-0.90, 0.46)
	Median	-0.90	-0.43
	Q1, Q3	-1.40, 0.00	-1.40, 0.49
	Min, Max	-2.1, 2.5	-2.4, 2.3

Table 14.20 ANCOVA analysis of change from baseline in weekly mean TVRSS in age group 18-<35 at Week 4, FAS

		Estimate		Difference to Placebo		
Treatment	n	LS mean	95% CI	LS mean	95% CI	P-value
Active	13	-0.567	-1.319, 0.186	-0.351	-1.338, 0.636	0.4719
Placebo	18	-0.215	-0.854, 0.424			

Table 14.21 Summary of weekly mean TVRSS and change from baseline in age group 35-<50 up to Week 4, FAS

Week	Statistic	Active N=81	Placebo N=79
Week -1	n	31	22
	Mean (SD)	3.89 (1.57)	3.75 (1.25)
	95% CI	(3.32, 4.47)	(3.20, 4.31)
	Median	4.00	3.42
	Q1, Q3	2.57, 5.00	2.60, 4.67
	Min, Max	1.2, 7.7	2.2, 6.0
Week 1	n	31	22
	Mean (SD)	3.40 (1.62)	3.58 (1.33)
	95% CI	(2.80, 3.99)	(2.99, 4.17)
	Median	3.14	3.13
	Q1, Q3	2.14, 4.67	2.86, 4.50
	Min, Max	0.9, 6.6	1.7, 7.0
Week 2	n	31	22
	Mean (SD)	3.18 (1.96)	3.45 (1.57)
	95% CI	(2.46, 3.90)	(2.76, 4.15)
	Median	2.86	3.07
	Q1, Q3	1.86, 4.00	2.29, 4.67
	Min, Max	0.7, 10.0	1.1, 6.2
Change from baseline, Week 2	n	31	22
	Mean (SD)	-0.71 (1.28)	-0.30 (1.44)
	95% CI	(-1.18, -0.24)	(-0.94, 0.34)
	Median	-0.77	-0.26
	Q1, Q3	-1.38, -0.20	-1.10, 0.31
	Min, Max	-3.0, 4.0	-3.6, 3.3
Week 3	n	31	22
	Mean (SD)	3.24 (1.77)	3.38 (1.43)
	95% CI	(2.60, 3.89)	(2.75, 4.02)
	Median	3.29	3.00
	Q1, Q3	2.00, 4.20	2.57, 4.50
	Min, Max	0.3, 7.0	0.9, 6.5
Change from baseline, Week 3	n	31	22
	Mean (SD)	-0.65 (1.43)	-0.37 (1.50)
	95% CI	(-1.18, -0.13)	(-1.04, 0.30)
	Median	-0.57	-0.38
	Q1, Q3	-1.50, 0.00	-1.17, 0.17
	Min, Max	-2.8, 4.6	-3.9, 4.2
Week 4	n	29	22
	Mean (SD)	3.43 (1.70)	3.38 (1.66)
	95% CI	(2.78, 4.07)	(2.65, 4.12)
	Median	3.00	3.42
	Q1, Q3	2.29, 5.00	1.67, 4.57
	Min, Max	0.1, 6.3	0.8, 6.3
Change from baseline, Week 4	n	29	22
	Mean (SD)	-0.52 (1.15)	-0.37 (1.49)
	95% CI	(-0.95, -0.08)	(-1.03, 0.29)

Week	Statistic	Active N=81	Placebo N=79
	Median	-0.67	-0.35
	Q1, Q3	-1.33, 0.43	-1.10, 0.33
	Min, Max	-2.7, 1.7	-3.9, 3.3

Table 14.22 ANCOVA analysis of change from baseline in weekly mean TVRSS in age group 35-<50 at Week 4, FAS

		Estimate		Difference to Placebo		
Treatment	n	LS mean	95% CI	LS mean	95% CI	P-value
Active	29	-0.496	-0.973, -0.019	-0.099	-0.826, 0.628	0.7855
Placebo	22	-0.397	-0.944, 0.151			

Table 14.23 Summary of weekly mean TVRSS and change from baseline in age group 50-65 up to Week 4, FAS

Week	Statistic	Active N=81	Placebo N=79
Week -1	n	37	39
	Mean (SD)	4.20 (1.80)	3.80 (1.52)
	95% CI	(3.60, 4.81)	(3.31, 4.29)
	Median	3.71	3.17
	Q1, Q3	2.67, 5.83	2.57, 4.67
	Min, Max	1.7, 8.7	1.5, 7.7
Week 1	n	37	39
	Mean (SD)	3.69 (1.70)	3.79 (1.63)
	95% CI	(3.12, 4.25)	(3.27, 4.32)
	Median	3.43	3.50
	Q1, Q3	2.29, 4.57	2.67, 4.83
	Min, Max	1.1, 8.3	1.4, 9.0
Week 2	n	37	39
	Mean (SD)	3.43 (1.78)	3.86 (1.65)
	95% CI	(2.84, 4.02)	(3.33, 4.40)
	Median	3.43	3.57
	Q1, Q3	2.00, 4.14	2.60, 4.71
	Min, Max	0.5, 8.3	1.5, 9.3
Change from baseline, Week 2	n	37	39
	Mean (SD)	-0.77 (1.72)	0.06 (1.05)
	95% CI	(-1.35, -0.20)	(-0.28, 0.40)
	Median	-0.38	0.00
	Q1, Q3	-1.48, 0.20	-0.57, 0.90
	Min, Max	-4.5, 2.6	-2.3, 1.9
Week 3	n	36	39
	Mean (SD)	3.47 (1.73)	3.64 (1.73)
	95% CI	(2.89, 4.06)	(3.08, 4.20)
	Median	3.21	3.29
	Q1, Q3	2.34, 4.79	2.57, 4.86

Week	Statistic	Active N=81	Placebo N=79
	Min, Max	0.9, 7.3	1.1, 8.8
Change from baseline, Week 3	n	36	39
	Mean (SD)	-0.65 (1.74)	-0.16 (1.50)
	95% CI	(-1.24, -0.06)	(-0.65, 0.33)
	Median	-0.27	-0.36
	Q1, Q3	-1.45, 0.74	-1.29, 0.71
	Min, Max	-5.1, 1.7	-2.7, 4.4
Week 4	n	36	39
	Mean (SD)	3.27 (1.37)	3.73 (1.79)
	95% CI	(2.81, 3.74)	(3.15, 4.31)
	Median	3.18	3.29
	Q1, Q3	2.31, 4.07	2.60, 4.80
	Min, Max	0.6, 6.0	1.5, 10.8
Change from baseline, Week 4	n	36	39
	Mean (SD)	-0.85 (1.66)	-0.07 (1.46)
	95% CI	(-1.42, -0.29)	(-0.55, 0.40)
	Median	-0.49	-0.07
	Q1, Q3	-1.63, 0.04	-1.00, 0.67
	Min, Max	-4.7, 2.3	-3.0, 4.1

Table 14.24 ANCOVA analysis of change from baseline in weekly mean TVRSS in age group 50-65 at Week 4, FAS

		Estimate		Difference to Placebo		
Treatment	n	LS mean	95% CI	LS mean	95% CI	P-value
Active	36	-0.773	-1.225, -0.320	-0.625	-1.254, 0.004	0.0515
Placebo	39	-0.148	-0.582, 0.287			

14.3.2 Secondary endpoints

Table 14.25 Summary of weekly mean TVRSS from Week 5 to Week 24, FAS

Week	Statistic	Active + Active N=81	Placebo + Active N=79
Week 5	n	77	77
	Mean (SD)	3.00 (1.45)	3.38 (1.68)
	95% CI	(2.67, 3.33)	(3.00, 3.76)
	Median	2.75	3.00
	Q1, Q3	2.00, 4.00	2.43, 4.14
	Min, Max	0.4, 6.5	0.3, 8.8
Change from baseline, Week 5	n	77	77
	Mean (SD)	-1.05 (1.65)	-0.45 (1.39)
	95% CI	(-1.43, -0.68)	(-0.77, -0.14)
	Median	-1.06	-0.43
	Q1, Q3	-1.94, 0.14	-1.40, 0.33
	Min, Max	-5.4, 2.4	-3.9, 3.4
Week 6	n	78	76
	Mean (SD)	2.75 (1.59)	3.42 (1.79)
	95% CI	(2.39, 3.10)	(3.01, 3.83)
	Median	2.58	3.18
	Q1, Q3	1.57, 3.57	2.31, 4.30
	Min, Max	0.3, 7.8	0.0, 10.7
Change from baseline, Week 6	n	78	76
	Mean (SD)	-1.31 (1.51)	-0.43 (1.56)
	95% CI	(-1.65, -0.96)	(-0.79, -0.07)
	Median	-1.14	-0.39
	Q1, Q3	-2.10, -0.17	-1.37, 0.49
	Min, Max	-5.5, 1.6	-4.8, 4.0
Week 7	n	78	74
	Mean (SD)	2.94 (1.60)	3.53 (1.82)
	95% CI	(2.58, 3.30)	(3.11, 3.95)
	Median	2.76	3.31
	Q1, Q3	1.86, 3.83	2.25, 4.57
	Min, Max	0.3, 8.0	0.0, 8.5
Change from baseline, Week 7	n	78	74
	Mean (SD)	-1.11 (1.57)	-0.30 (1.76)
	95% CI	(-1.46, -0.76)	(-0.71, 0.11)
	Median	-0.93	-0.29
	Q1, Q3	-1.86, 0.03	-1.43, 0.93
	Min, Max	-4.7, 1.9	-4.8, 3.0
Week 8	n	73	75
	Mean (SD)	2.75 (1.43)	3.28 (1.84)
	95% CI	(2.41, 3.08)	(2.85, 3.70)
	Median	2.57	3.00
	Q1, Q3	1.75, 3.80	2.14, 4.25
	Min, Max	0.0, 6.0	0.3, 9.6
Change from baseline, Week 8	n	73	75
	Mean (SD)	-1.33 (1.63)	-0.57 (1.77)

Week	Statistic	Active + Active N=81	Placebo + Active N=79
	95% CI	(-1.71, -0.95)	(-0.98, -0.17)
	Median	-1.17	-0.52
	Q1, Q3	-2.14, -0.08	-1.60, 0.52
	Min, Max	-5.3, 1.5	-5.5, 3.7
Week 12	n	77	73
	Mean (SD)	2.90 (1.63)	3.29 (1.89)
	95% CI	(2.53, 3.27)	(2.85, 3.74)
	Median	2.25	3.00
	Q1, Q3	1.83, 4.14	2.00, 4.20
	Min, Max	0.0, 7.5	0.0, 8.7
Change from baseline, Week 12	n	77	73
	Mean (SD)	-1.15 (1.77)	-0.56 (1.94)
	95% CI	(-1.55, -0.75)	(-1.01, -0.10)
	Median	-1.00	-0.50
	Q1, Q3	-1.90, 0.00	-1.83, 0.67
	Min, Max	-6.2, 2.0	-5.8, 4.3
Week 24	n	70	68
	Mean (SD)	3.28 (1.88)	2.68 (1.79)
	95% CI	(2.83, 3.73)	(2.25, 3.12)
	Median	3.00	2.63
	Q1, Q3	2.00, 4.80	1.23, 3.45
	Min, Max	0.2, 7.6	0.0, 9.5
Change from baseline, Week 24	n	70	68
	Mean (SD)	-0.81 (1.85)	-1.06 (1.66)
	95% CI	(-1.25, -0.37)	(-1.46, -0.65)
	Median	-0.79	-0.83
	Q1, Q3	-1.83, 0.20	-2.50, 0.02
	Min, Max	-5.9, 4.8	-5.1, 3.7

Table 14.26 Summary of weekly mean TVRSS Week 5 to Week 24, PPAS

Visit	Statistic	Active + Active N=67	Placebo + Active N=63
Week 5	n	64	61
	Mean (SD)	3.07 (1.52)	3.49 (1.80)
	95% CI	(2.69, 3.45)	(3.03, 3.96)
	Median	2.73	3.36
	Q1, Q3	2.00, 4.06	2.43, 4.29
	Min, Max	0.4, 6.5	0.3, 8.8
Change from baseline, Week 5	n	64	61
	Mean (SD)	-1.16 (1.60)	-0.48 (1.44)
	95% CI	(-1.56, -0.76)	(-0.85, -0.12)
	Median	-1.14	-0.43
	Q1, Q3	-1.90, 0.01	-1.46, 0.33
	Min, Max	-5.4, 2.4	-3.9, 3.4
Week 6	n	65	60
	Mean (SD)	2.85 (1.60)	3.49 (1.86)
	95% CI	(2.45, 3.25)	(3.01, 3.97)
	Median	2.67	3.20
	Q1, Q3	1.75, 3.86	2.43, 4.50
	Min, Max	0.3, 7.8	0.0, 10.7
Change from baseline, Week 6	n	65	60
	Mean (SD)	-1.37 (1.52)	-0.51 (1.58)
	95% CI	(-1.75, -1.00)	(-0.92, -0.10)
	Median	-1.17	-0.44
	Q1, Q3	-2.14, -0.17	-1.42, 0.49
	Min, Max	-5.5, 1.5	-4.8, 4.0
Week 7	n	65	59
	Mean (SD)	3.05 (1.66)	3.61 (1.75)
	95% CI	(2.64, 3.47)	(3.15, 4.06)
	Median	2.57	3.43
	Q1, Q3	2.00, 4.00	2.40, 4.57
	Min, Max	0.3, 8.0	0.0, 8.5
Change from baseline, Week 7	n	65	59
	Mean (SD)	-1.17 (1.63)	-0.37 (1.72)
	95% CI	(-1.57, -0.76)	(-0.82, 0.08)
	Median	-1.00	-0.30
	Q1, Q3	-2.29, 0.03	-1.43, 0.75
	Min, Max	-4.7, 1.9	-4.8, 2.5
Week 8	n	60	60
	Mean (SD)	2.87 (1.47)	3.43 (1.92)
	95% CI	(2.49, 3.25)	(2.94, 3.93)
	Median	2.62	3.07
	Q1, Q3	1.80, 4.17	2.15, 4.33
	Min, Max	0.4, 6.0	0.3, 9.6
Change from baseline, Week 8	n	60	60
	Mean (SD)	-1.40 (1.67)	-0.57 (1.89)
	95% CI	(-1.84, -0.97)	(-1.06, -0.08)
	Median	-1.20	-0.51

Visit	Statistic	Active + Active N=67	Placebo + Active N=63
	Q1, Q3	-2.69, -0.07	-1.65, 0.51
	Min, Max	-5.3, 1.1	-5.5, 3.7
Week 12	n	64	58
	Mean (SD)	3.02 (1.68)	3.43 (1.83)
	95% CI	(2.60, 3.44)	(2.95, 3.91)
	Median	2.29	3.00
	Q1, Q3	2.00, 4.55	2.20, 4.33
	Min, Max	0.0, 7.5	0.3, 7.8
Change from baseline, Week 12	n	64	58
	Mean (SD)	-1.21 (1.81)	-0.57 (1.91)
	95% CI	(-1.66, -0.76)	(-1.08, -0.07)
	Median	-0.93	-0.50
	Q1, Q3	-2.14, 0.03	-1.83, 0.43
	Min, Max	-6.2, 2.0	-5.8, 4.3
Week 24	n	58	53
	Mean (SD)	3.17 (1.92)	2.76 (1.84)
	95% CI	(2.66, 3.67)	(2.25, 3.27)
	Median	2.50	2.67
	Q1, Q3	2.00, 4.80	1.00, 4.00
	Min, Max	0.2, 7.6	0.0, 9.5
Change from baseline, Week 24	n	58	53
	Mean (SD)	-1.09 (1.68)	-1.11 (1.67)
	95% CI	(-1.53, -0.65)	(-1.57, -0.65)
	Median	-1.00	-0.83
	Q1, Q3	-2.04, 0.00	-2.50, 0.00
	Min, Max	-5.9, 2.3	-5.1, 3.7

Table 14.27 ANCOVA analysis of weekly mean TVRSS at Weeks 8, 12 and 24, PPAS

		Estimate			Difference to one active treatment		
Visit	Treatment	n	LS mean	95% CI	LS mean	95% CI	P-value
Week 8 (Visit 4)	Active + Active	60	-1.329	-1.733, -0.926	-0.687	-1.259, -0.115	0.0190
	Placebo + Active	60	-0.642	-1.046, -0.239			
Week 12	Active + Active	64	-1.145	-1.550, -0.740	-0.502	-1.090, 0.087	0.0941
	Placebo + Active	58	-0.643	-1.069, -0.217			
Week 24 (Visit 5)	Active + Active	58	-1.030	-1.452, -0.609	0.150	-0.462, 0.763	0.6275
	Placebo + Active	53	-1.181	-1.622, -0.739			

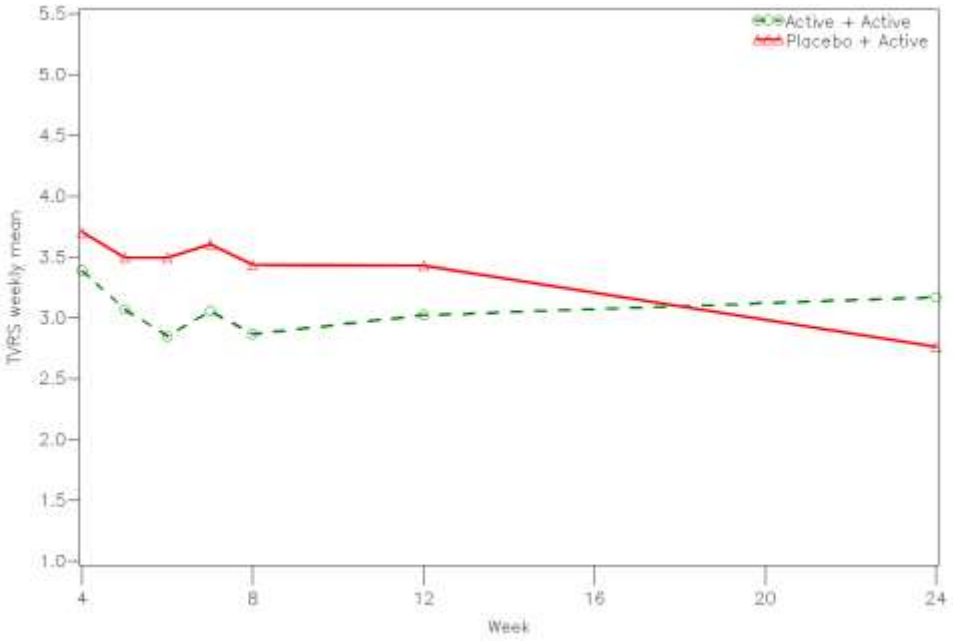


Figure 14.3 Weekly mean TVRS by treatment from Week 4 to 24, PPAS

Table 14.28 Summary of weekly mean TVRSS Week 5 to 24, FAS (before and after interim analysis)

Week	Statistic	Old Active + Active N=49	Low amplitude control + Active N=47	New Active + Active N=32	Placebo + Active N=79
Week 5	n	45	44	32	77
	Mean (SD)	2.97 (1.50)	2.78 (1.28)	3.04 (1.40)	3.38 (1.68)
	95% CI	(2.52, 3.42)	(2.39, 3.17)	(2.54, 3.55)	(3.00, 3.76)
	Median	2.57	2.93	3.00	3.00
	Q1, Q3	2.00, 3.67	2.00, 3.57	2.07, 4.00	2.43, 4.14
	Min, Max	0.4, 6.5	0.3, 6.6	0.7, 6.3	0.3, 8.8
Change from baseline, Week 5	n	45	44	32	77
	Mean (SD)	-0.97 (1.76)	-1.30 (1.48)	-1.17 (1.49)	-0.45 (1.39)
	95% CI	(-1.50, -0.44)	(-1.75, -0.85)	(-1.71, -0.63)	(-0.77, -0.14)
	Median	-1.00	-1.07	-1.15	-0.43
	Q1, Q3	-1.81, 0.20	-2.15, -0.60	-1.98, -0.07	-1.40, 0.33
	Min, Max	-5.4, 2.4	-5.3, 2.1	-4.3, 1.7	-3.9, 3.4
Week 6	n	47	44	31	76
	Mean (SD)	2.57 (1.51)	2.85 (1.46)	3.01 (1.68)	3.42 (1.79)
	95% CI	(2.13, 3.02)	(2.41, 3.29)	(2.39, 3.62)	(3.01, 3.83)
	Median	2.43	2.71	2.71	3.18
	Q1, Q3	1.43, 3.14	1.76, 3.83	1.86, 4.25	2.31, 4.30
	Min, Max	0.3, 6.3	0.6, 6.6	0.6, 7.8	0.0, 10.7
Change from baseline, Week 6	n	47	44	31	76
	Mean (SD)	-1.36 (1.49)	-1.24 (1.36)	-1.23 (1.57)	-0.43 (1.56)
	95% CI	(-1.79, -0.92)	(-1.65, -0.83)	(-1.81, -0.65)	(-0.79, -0.07)

Week	Statistic	Old Active + Active N=49	Low amplitude control + Active N=47	New Active + Active N=32	Placebo + Active N=79
	Median	-1.00	-1.06	-1.43	-0.39
	Q1, Q3	-2.00, -0.14	-2.33, -0.36	-2.14, -0.29	-1.37, 0.49
	Min, Max	-5.5, 1.4	-4.0, 2.1	-4.0, 1.6	-4.8, 4.0
Week 7	n	47	44	31	74
	Mean (SD)	2.90 (1.67)	2.92 (1.46)	3.00 (1.51)	3.53 (1.82)
	95% CI	(2.41, 3.39)	(2.48, 3.37)	(2.45, 3.55)	(3.11, 3.95)
	Median	2.57	2.77	2.86	3.31
	Q1, Q3	1.83, 3.29	1.86, 3.57	2.00, 4.29	2.25, 4.57
	Min, Max	0.3, 8.0	0.6, 7.0	0.3, 6.1	0.0, 8.5
Change from baseline, Week 7	n	47	44	31	74
	Mean (SD)	-1.03 (1.49)	-1.17 (1.45)	-1.24 (1.70)	-0.30 (1.76)
	95% CI	(-1.47, -0.59)	(-1.61, -0.73)	(-1.86, -0.62)	(-0.71, 0.11)
	Median	-1.00	-0.99	-0.86	-0.29
	Q1, Q3	-1.71, 0.19	-2.23, -0.18	-2.80, 0.00	-1.43, 0.93
	Min, Max	-4.7, 1.9	-4.2, 2.5	-4.4, 1.6	-4.8, 3.0
Week 8	n	42	42	31	75
	Mean (SD)	2.59 (1.39)	3.01 (1.48)	2.96 (1.48)	3.28 (1.84)
	95% CI	(2.16, 3.02)	(2.54, 3.47)	(2.42, 3.51)	(2.85, 3.70)
	Median	2.33	2.77	3.33	3.00
	Q1, Q3	1.75, 3.29	2.00, 4.00	1.71, 4.33	2.14, 4.25
	Min, Max	0.4, 5.8	0.7, 7.0	0.0, 6.0	0.3, 9.6
Change from baseline, Week 8	n	42	42	31	75
	Mean (SD)	-1.37 (1.64)	-1.11 (1.50)	-1.28 (1.64)	-0.57 (1.77)
	95% CI	(-1.88, -0.86)	(-1.58, -0.65)	(-1.88, -0.67)	(-0.98, -0.17)
	Median	-1.33	-1.05	-1.00	-0.52
	Q1, Q3	-2.00, -0.14	-2.00, -0.29	-2.71, 0.33	-1.60, 0.52
	Min, Max	-5.3, 1.5	-4.1, 2.5	-4.3, 1.0	-5.5, 3.7
Week 12	n	46	42	31	73
	Mean (SD)	2.79 (1.69)	2.83 (1.82)	3.07 (1.56)	3.29 (1.89)
	95% CI	(2.29, 3.29)	(2.26, 3.39)	(2.50, 3.64)	(2.85, 3.74)
	Median	2.08	2.29	2.67	3.00
	Q1, Q3	1.80, 4.00	1.33, 3.83	2.00, 4.60	2.00, 4.20
	Min, Max	0.0, 7.5	0.7, 8.0	0.5, 6.3	0.0, 8.7
Change from baseline, Week 12	n	46	42	31	73
	Mean (SD)	-1.18 (1.72)	-1.27 (2.04)	-1.11 (1.87)	-0.56 (1.94)
	95% CI	(-1.69, -0.67)	(-1.90, -0.63)	(-1.80, -0.43)	(-1.01, -0.10)
	Median	-0.83	-1.00	-1.00	-0.50
	Q1, Q3	-2.14, -0.08	-2.33, -0.66	-1.90, 0.17	-1.83, 0.67
	Min, Max	-5.2, 2.0	-5.3, 5.8	-6.2, 2.0	-5.8, 4.3
Week 24	n	43	40	27	68
	Mean (SD)	3.31 (1.91)	2.98 (1.65)	3.22 (1.87)	2.68 (1.79)
	95% CI	(2.73, 3.90)	(2.45, 3.51)	(2.47, 3.96)	(2.25, 3.12)
	Median	2.50	2.50	3.00	2.63
	Q1, Q3	2.00, 4.80	2.00, 4.13	2.00, 5.00	1.23, 3.45
	Min, Max	0.3, 7.6	0.7, 8.0	0.2, 7.0	0.0, 9.5
Change from baseline, Week 24	n	43	40	27	68
	Mean (SD)	-0.70 (2.06)	-1.07 (1.92)	-0.99 (1.48)	-1.06 (1.66)

Week	Statistic	Old Active + Active N=49	Low amplitude control + Active N=47	New Active + Active N=32	Placebo + Active N=79
	95% CI	(-1.33, -0.06)	(-1.69, -0.46)	(-1.58, -0.41)	(-1.46, -0.65)
	Median	-0.40	-0.70	-1.00	-0.83
	Q1, Q3	-1.83, 0.20	-2.13, -0.16	-2.03, 0.33	-2.50, 0.02
	Min, Max	-5.9, 4.8	-6.1, 4.1	-3.7, 2.3	-5.1, 3.7

Table 14.29 Summary of weekly mean TVRSS Week 5 to Week 24, PPAS (before and after interim analysis)

Week	Statistic	Old Active + Active N=40	Low amplitude control + Active N=40	New Active + Active N=27	Placebo + Active N=63
Week 5	N	37	39	27	61
	Mean (SD)	2.98 (1.59)	2.86 (1.26)	3.19 (1.45)	3.49 (1.80)
	95% CI	(2.45, 3.51)	(2.45, 3.27)	(2.61, 3.76)	(3.03, 3.96)
	Median	2.33	3.00	3.14	3.36
	Q1, Q3	2.00, 3.43	2.00, 3.57	2.14, 4.13	2.43, 4.29
	Min, Max	0.4, 6.5	0.3, 6.6	0.7, 6.3	0.3, 8.8
Change from baseline, Week 5	n	37	39	27	61
	Mean (SD)	-1.15 (1.67)	-1.44 (1.46)	-1.17 (1.54)	-0.48 (1.44)
	95% CI	(-1.71, -0.60)	(-1.91, -0.97)	(-1.77, -0.56)	(-0.85, -0.12)
	Median	-1.14	-1.08	-1.13	-0.43
	Q1, Q3	-1.81, 0.14	-2.50, -0.69	-2.00, 0.00	-1.46, 0.33
	Min, Max	-5.4, 2.4	-5.3, 2.1	-4.3, 1.7	-3.9, 3.4
Week 6	n	39	39	26	60
	Mean (SD)	2.71 (1.56)	2.97 (1.47)	3.05 (1.67)	3.49 (1.86)
	95% CI	(2.21, 3.22)	(2.50, 3.45)	(2.38, 3.73)	(3.01, 3.97)
	Median	2.67	2.71	2.69	3.20
	Q1, Q3	1.57, 3.17	2.00, 4.00	2.00, 4.25	2.43, 4.50
	Min, Max	0.3, 6.3	0.6, 6.6	0.6, 7.8	0.0, 10.7
Change from baseline, Week 6	n	39	39	26	60
	Mean (SD)	-1.40 (1.47)	-1.34 (1.39)	-1.33 (1.62)	-0.51 (1.58)
	95% CI	(-1.88, -0.92)	(-1.79, -0.89)	(-1.99, -0.68)	(-0.92, -0.10)
	Median	-1.00	-1.29	-1.61	-0.44
	Q1, Q3	-2.00, -0.14	-2.43, -0.43	-2.50, -0.29	-1.42, 0.49
	Min, Max	-5.5, 0.7	-4.0, 2.1	-4.0, 1.5	-4.8, 4.0
Week 7	n	39	39	26	59
	Mean (SD)	3.02 (1.75)	3.02 (1.41)	3.11 (1.55)	3.61 (1.75)
	95% CI	(2.45, 3.58)	(2.56, 3.47)	(2.49, 3.74)	(3.15, 4.06)
	Median	2.50	2.83	2.90	3.43
	Q1, Q3	1.86, 3.33	2.00, 3.57	2.00, 4.40	2.40, 4.57
	Min, Max	0.3, 8.0	1.0, 7.0	0.3, 6.1	0.0, 8.5
Change from baseline, Week 7	n	39	39	26	59
	Mean (SD)	-1.09 (1.48)	-1.29 (1.47)	-1.28 (1.85)	-0.37 (1.72)
	95% CI	(-1.57, -0.62)	(-1.77, -0.82)	(-2.02, -0.53)	(-0.82, 0.08)
	Median	-1.14	-1.29	-0.62	-0.30
	Q1, Q3	-1.71, 0.03	-2.43, -0.29	-3.12, 0.14	-1.43, 0.75
	Min, Max	-4.7, 1.9	-4.2, 2.5	-4.4, 1.6	-4.8, 2.5
Week 8	n	34	38	26	60

Week	Statistic	Old Active + Active N=40	Low amplitude control + Active N=40	New Active + Active N=27	Placebo + Active N=63
	Mean (SD)	2.67 (1.48)	3.07 (1.40)	3.13 (1.43)	3.43 (1.92)
	95% CI	(2.15, 3.18)	(2.61, 3.53)	(2.55, 3.71)	(2.94, 3.93)
	Median	2.45	2.83	3.33	3.07
	Q1, Q3	1.75, 3.33	2.00, 4.00	2.00, 4.43	2.15, 4.33
	Min, Max	0.4, 5.8	1.0, 7.0	1.0, 6.0	0.3, 9.6
Change from baseline, Week 8	n	34	38	26	60
	Mean (SD)	-1.51 (1.61)	-1.22 (1.53)	-1.26 (1.77)	-0.57 (1.89)
	95% CI	(-2.08, -0.95)	(-1.72, -0.71)	(-1.97, -0.55)	(-1.06, -0.08)
	Median	-1.43	-1.27	-0.96	-0.51
	Q1, Q3	-2.00, -0.25	-2.17, -0.29	-2.79, 0.40	-1.65, 0.51
	Min, Max	-5.3, 1.1	-4.1, 2.5	-4.3, 1.0	-5.5, 3.7
Week 12	n	38	38	26	58
	Mean (SD)	2.88 (1.77)	2.83 (1.64)	3.23 (1.55)	3.43 (1.83)
	95% CI	(2.30, 3.46)	(2.30, 3.37)	(2.60, 3.85)	(2.95, 3.91)
	Median	2.18	2.37	2.58	3.00
	Q1, Q3	1.83, 4.00	1.67, 3.83	2.00, 4.67	2.20, 4.33
	Min, Max	0.0, 7.5	0.7, 8.0	0.7, 6.3	0.3, 7.8
Change from baseline, Week 12	n	38	38	26	58
	Mean (SD)	-1.28 (1.65)	-1.45 (1.99)	-1.09 (2.04)	-0.57 (1.91)
	95% CI	(-1.83, -0.74)	(-2.10, -0.79)	(-1.92, -0.27)	(-1.08, -0.07)
	Median	-1.00	-1.25	-0.83	-0.50
	Q1, Q3	-2.29, -0.14	-2.60, -0.69	-2.00, 0.21	-1.83, 0.43
	Min, Max	-5.2, 1.7	-5.3, 5.8	-6.2, 2.0	-5.8, 4.3
Week 24	n	36	36	22	53
	Mean (SD)	3.07 (1.87)	3.17 (1.62)	3.32 (2.02)	2.76 (1.84)
	95% CI	(2.44, 3.71)	(2.62, 3.72)	(2.43, 4.22)	(2.25, 3.27)
	Median	2.37	2.80	3.00	2.67
	Q1, Q3	1.83, 4.08	2.00, 4.29	2.00, 5.00	1.00, 4.00
	Min, Max	0.3, 7.6	0.7, 8.0	0.2, 7.0	0.0, 9.5
Change from baseline, Week 24	n	36	36	22	53
	Mean (SD)	-1.11 (1.79)	-1.07 (1.96)	-1.06 (1.53)	-1.11 (1.67)
	95% CI	(-1.72, -0.51)	(-1.74, -0.41)	(-1.73, -0.38)	(-1.57, -0.65)
	Median	-0.83	-0.70	-1.15	-0.83
	Q1, Q3	-2.11, 0.00	-2.13, -0.27	-2.03, 0.33	-2.50, 0.00
	Min, Max	-5.9, 2.3	-6.1, 4.1	-3.7, 2.3	-5.1, 3.7

Table 14.30 Weekly median individual symptom score by week up to Week 4, FAS

Parameter	Week	Score	Active N=81 n (%)	Active N=81 95% CI	Placebo N=79 n (%)	Placebo N=79 95% CI
Nasal Congestion Symptom Score median	Week -1	None	0	(0.0%, 4.5%)	0	(0.0%, 4.6%)
		Mild	12 (14.8%)	(7.9%, 24.4%)	15 (19.0%)	(11.0%, 29.4%)
		Moderate	53 (65.4%)	(54.0%, 75.7%)	47 (59.5%)	(47.9%, 70.4%)
		Severe	16 (19.8%)	(11.7%, 30.1%)	17 (21.5%)	(13.1%, 32.2%)
	Week 1	None	2 (2.5%)	(0.3%, 8.6%)	2 (2.5%)	(0.3%, 8.8%)
		Mild	25 (30.9%)	(21.1%, 42.1%)	23 (29.1%)	(19.4%, 40.4%)
		Moderate	46 (56.8%)	(45.3%, 67.8%)	42 (53.2%)	(41.6%, 64.5%)
		Severe	8 (9.9%)	(4.4%, 18.5%)	12 (15.2%)	(8.1%, 25.0%)
	Week 2	None	3 (3.7%)	(0.8%, 10.4%)	2 (2.5%)	(0.3%, 8.8%)
		Mild	33 (40.7%)	(29.9%, 52.2%)	23 (29.1%)	(19.4%, 40.4%)
		Moderate	37 (45.7%)	(34.6%, 57.1%)	43 (54.4%)	(42.8%, 65.7%)
		Severe	8 (9.9%)	(4.4%, 18.5%)	11 (13.9%)	(7.2%, 23.5%)
	Week 3	None	4 (5.0%)	(1.4%, 12.3%)	2 (2.5%)	(0.3%, 8.8%)
		Mild	31 (38.8%)	(28.1%, 50.3%)	22 (27.8%)	(18.3%, 39.1%)
		Moderate	33 (41.3%)	(30.4%, 52.8%)	43 (54.4%)	(42.8%, 65.7%)
		Severe	12 (15.0%)	(8.0%, 24.7%)	12 (15.2%)	(8.1%, 25.0%)
	Week 4	None	4 (5.1%)	(1.4%, 12.6%)	3 (3.8%)	(0.8%, 10.7%)
		Mild	27 (34.6%)	(24.2%, 46.2%)	17 (21.5%)	(13.1%, 32.2%)
		Moderate	42 (53.8%)	(42.2%, 65.2%)	48 (60.8%)	(49.1%, 71.6%)
		Severe	5 (6.4%)	(2.1%, 14.3%)	11 (13.9%)	(7.2%, 23.5%)
Rhinorrhea Symptom Score median	Week -1	None	33 (40.7%)	(29.9%, 52.2%)	39 (49.4%)	(37.9%, 60.9%)
		Mild	38 (46.9%)	(35.7%, 58.3%)	21 (26.6%)	(17.3%, 37.7%)
		Moderate	9 (11.1%)	(5.2%, 20.0%)	18 (22.8%)	(14.1%, 33.6%)
		Severe	1 (1.2%)	(0.0%, 6.7%)	1 (1.3%)	(0.0%, 6.9%)
	Week 1	None	37 (45.7%)	(34.6%, 57.1%)	32 (40.5%)	(29.6%, 52.1%)
		Mild	36 (44.4%)	(33.4%, 55.9%)	35 (44.3%)	(33.1%, 55.9%)
		Moderate	7 (8.6%)	(3.5%, 17.0%)	12 (15.2%)	(8.1%, 25.0%)
		Severe	1 (1.2%)	(0.0%, 6.7%)	0	(0.0%, 4.6%)
	Week 2	None	45 (55.6%)	(44.1%, 66.6%)	37 (46.8%)	(35.5%, 58.4%)
		Mild	25 (30.9%)	(21.1%, 42.1%)	28 (35.4%)	(25.0%, 47.0%)
		Moderate	10 (12.3%)	(6.1%, 21.5%)	11 (13.9%)	(7.2%, 23.5%)
		Severe	1 (1.2%)	(0.0%, 6.7%)	3 (3.8%)	(0.8%, 10.7%)
	Week 3	None	43 (53.8%)	(42.2%, 65.0%)	36 (45.6%)	(34.3%, 57.2%)
		Mild	26 (32.5%)	(22.4%, 43.9%)	29 (36.7%)	(26.1%, 48.3%)
		Moderate	10 (12.5%)	(6.2%, 21.8%)	13 (16.5%)	(9.1%, 26.5%)
		Severe	1 (1.3%)	(0.0%, 6.8%)	1 (1.3%)	(0.0%, 6.9%)
	Week 4	None	40 (51.3%)	(39.7%, 62.8%)	38 (48.1%)	(36.7%, 59.6%)
		Mild	34 (43.6%)	(32.4%, 55.3%)	31 (39.2%)	(28.4%, 50.9%)
		Moderate	4 (5.1%)	(1.4%, 12.6%)	7 (8.9%)	(3.6%, 17.4%)
		Severe	0	(0.0%, 4.6%)	3 (3.8%)	(0.8%, 10.7%)
Postnasal Drip Symptom Score median	Week -1	None	36 (44.4%)	(33.4%, 55.9%)	33 (41.8%)	(30.8%, 53.4%)
		Mild	29 (35.8%)	(25.4%, 47.2%)	35 (44.3%)	(33.1%, 55.9%)
		Moderate	14 (17.3%)	(9.8%, 27.3%)	11 (13.9%)	(7.2%, 23.5%)
		Severe	2 (2.5%)	(0.3%, 8.6%)	0	(0.0%, 4.6%)

Parameter	Week	Score	Active N=81 n (%)	Active N=81 95% CI	Placebo N=79 n (%)	Placebo N=79 95% CI
	Week 1	None	39 (48.1%)	(36.9%, 59.5%)	36 (45.6%)	(34.3%, 57.2%)
		Mild	25 (30.9%)	(21.1%, 42.1%)	29 (36.7%)	(26.1%, 48.3%)
		Moderate	14 (17.3%)	(9.8%, 27.3%)	13 (16.5%)	(9.1%, 26.5%)
		Severe	3 (3.7%)	(0.8%, 10.4%)	1 (1.3%)	(0.0%, 6.9%)
	Week 2	None	39 (48.1%)	(36.9%, 59.5%)	35 (44.3%)	(33.1%, 55.9%)
		Mild	30 (37.0%)	(26.6%, 48.5%)	28 (35.4%)	(25.0%, 47.0%)
		Moderate	10 (12.3%)	(6.1%, 21.5%)	15 (19.0%)	(11.0%, 29.4%)
		Severe	2 (2.5%)	(0.3%, 8.6%)	1 (1.3%)	(0.0%, 6.9%)
	Week 3	None	35 (43.8%)	(32.7%, 55.3%)	39 (49.4%)	(37.9%, 60.9%)
		Mild	31 (38.8%)	(28.1%, 50.3%)	27 (34.2%)	(23.9%, 45.7%)
		Moderate	12 (15.0%)	(8.0%, 24.7%)	11 (13.9%)	(7.2%, 23.5%)
		Severe	2 (2.5%)	(0.3%, 8.7%)	2 (2.5%)	(0.3%, 8.8%)
	Week 4	None	34 (43.6%)	(32.4%, 55.3%)	39 (49.4%)	(37.9%, 60.9%)
		Mild	33 (42.3%)	(31.2%, 54.0%)	24 (30.4%)	(20.5%, 41.8%)
		Moderate	8 (10.3%)	(4.5%, 19.2%)	15 (19.0%)	(11.0%, 29.4%)
		Severe	3 (3.8%)	(0.8%, 10.8%)	1 (1.3%)	(0.0%, 6.9%)
Sneezing Symptom Score median	Week -1	None	50 (61.7%)	(50.3%, 72.3%)	58 (73.4%)	(62.3%, 82.7%)
		Mild	24 (29.6%)	(20.0%, 40.8%)	20 (25.3%)	(16.2%, 36.4%)
		Moderate	7 (8.6%)	(3.5%, 17.0%)	1 (1.3%)	(0.0%, 6.9%)
		Severe	0	(0.0%, 4.5%)	0	(0.0%, 4.6%)
	Week 1	None	57 (70.4%)	(59.2%, 80.0%)	54 (68.4%)	(56.9%, 78.4%)
		Mild	21 (25.9%)	(16.8%, 36.9%)	23 (29.1%)	(19.4%, 40.4%)
		Moderate	3 (3.7%)	(0.8%, 10.4%)	2 (2.5%)	(0.3%, 8.8%)
		Severe	0	(0.0%, 4.5%)	0	(0.0%, 4.6%)
	Week 2	None	51 (63.0%)	(51.5%, 73.4%)	51 (64.6%)	(53.0%, 75.0%)
		Mild	26 (32.1%)	(22.2%, 43.4%)	24 (30.4%)	(20.5%, 41.8%)
		Moderate	4 (4.9%)	(1.4%, 12.2%)	3 (3.8%)	(0.8%, 10.7%)
		Severe	0	(0.0%, 4.5%)	1 (1.3%)	(0.0%, 6.9%)
	Week 3	None	54 (67.5%)	(56.1%, 77.6%)	58 (73.4%)	(62.3%, 82.7%)
		Mild	21 (26.3%)	(17.0%, 37.3%)	16 (20.3%)	(12.0%, 30.8%)
		Moderate	4 (5.0%)	(1.4%, 12.3%)	5 (6.3%)	(2.1%, 14.2%)
		Severe	1 (1.3%)	(0.0%, 6.8%)	0	(0.0%, 4.6%)
	Week 4	None	50 (64.1%)	(52.4%, 74.7%)	54 (68.4%)	(56.9%, 78.4%)
		Mild	21 (26.9%)	(17.5%, 38.2%)	21 (26.6%)	(17.3%, 37.7%)
		Moderate	7 (9.0%)	(3.7%, 17.6%)	3 (3.8%)	(0.8%, 10.7%)
		Severe	0	(0.0%, 4.6%)	1 (1.3%)	(0.0%, 6.9%)

Table 14.31 Shift from baseline to Week 4 in weekly median individual symptom scores, FAS

		Active N=81					Placebo N=79				
	Post-baseline	Baseline					Baseline				
		None	Mild	Moderate	Severe	Total	None	Mild	Moderate	Severe	Total
Nasal Congestion Symptom Score	None	0	2 (2.6%)	2 (2.6%)	0	4 (5.1%)	0	1 (1.3%)	1 (1.3%)	1 (1.3%)	3 (3.8%)
	Mild	0	6 (7.7%)	17 (21.8%)	4 (5.1%)	27 (34.6%)	0	9 (11.4%)	6 (7.6%)	2 (2.5%)	17 (21.5%)
	Moderate	0	3 (3.8%)	31 (39.7%)	8 (10.3%)	42 (53.8%)	0	5 (6.3%)	37 (46.8%)	6 (7.6%)	48 (60.8%)
	Severe	0	0	2 (2.6%)	3 (3.8%)	5 (6.4%)	0	0	3 (3.8%)	8 (10.1%)	11 (13.9%)
	Total	0	11 (14.1%)	52 (66.7%)	15 (19.2%)	78 (100.0%)	0	15 (19.0%)	47 (59.5%)	17 (21.5%)	79 (100.0%)
Rhinorrhea Symptom Score	None	29 (37.2%)	4 (5.1%)	0	1 (1.3%)	34 (43.6%)	30 (38.0%)	8 (10.1%)	1 (1.3%)	0	39 (49.4%)
	Mild	5 (6.4%)	21 (26.9%)	7 (9.0%)	0	33 (42.3%)	2 (2.5%)	16 (20.3%)	6 (7.6%)	0	24 (30.4%)
	Moderate	0	3 (3.8%)	4 (5.1%)	1 (1.3%)	8 (10.3%)	1 (1.3%)	10 (12.7%)	4 (5.1%)	0	15 (19.0%)
	Severe	0	0	3 (3.8%)	0	3 (3.8%)	0	1 (1.3%)	0	0	1 (1.3%)
	Total	34 (43.6%)	28 (35.9%)	14 (17.9%)	2 (2.6%)	78 (100.0%)	33 (41.8%)	35 (44.3%)	11 (13.9%)	0	79 (100.0%)
Postnasal Drip Symptom Score	None	27 (34.6%)	13 (16.7%)	0	0	40 (51.3%)	30 (38.0%)	6 (7.6%)	2 (2.5%)	0	38 (48.1%)
	Mild	6 (7.7%)	22 (28.2%)	6 (7.7%)	0	34 (43.6%)	9 (11.4%)	13 (16.5%)	9 (11.4%)	0	31 (39.2%)
	Moderate	0	1 (1.3%)	2 (2.6%)	1 (1.3%)	4 (5.1%)	0	2 (2.5%)	5 (6.3%)	0	7 (8.9%)
	Severe	0	0	0	0	0	0	0	2 (2.5%)	1 (1.3%)	3 (3.8%)
	Total	33 (42.3%)	36 (46.2%)	8 (10.3%)	1 (1.3%)	78 (100.0%)	39 (49.4%)	21 (26.6%)	18 (22.8%)	1 (1.3%)	79 (100.0%)
Sneezing Symptom Score	None	42 (53.8%)	7 (9.0%)	1 (1.3%)	0	50 (64.1%)	45 (57.0%)	9 (11.4%)	0	0	54 (68.4%)
	Mild	4 (5.1%)	14 (17.9%)	3 (3.8%)	0	21 (26.9%)	11 (13.9%)	10 (12.7%)	0	0	21 (26.6%)
	Moderate	2 (2.6%)	3 (3.8%)	2 (2.6%)	0	7 (9.0%)	2 (2.5%)	1 (1.3%)	0	0	3 (3.8%)
	Severe	0	0	0	0	0	0	0	1 (1.3%)	0	1 (1.3%)
	Total	48 (61.5%)	24 (30.8%)	6 (7.7%)	0	78 (100.0%)	58 (73.4%)	20 (25.3%)	1 (1.3%)	0	79 (100.0%)

Percentages are based on the number of subjects with a non-missing value before and after treatment within each treatment group.

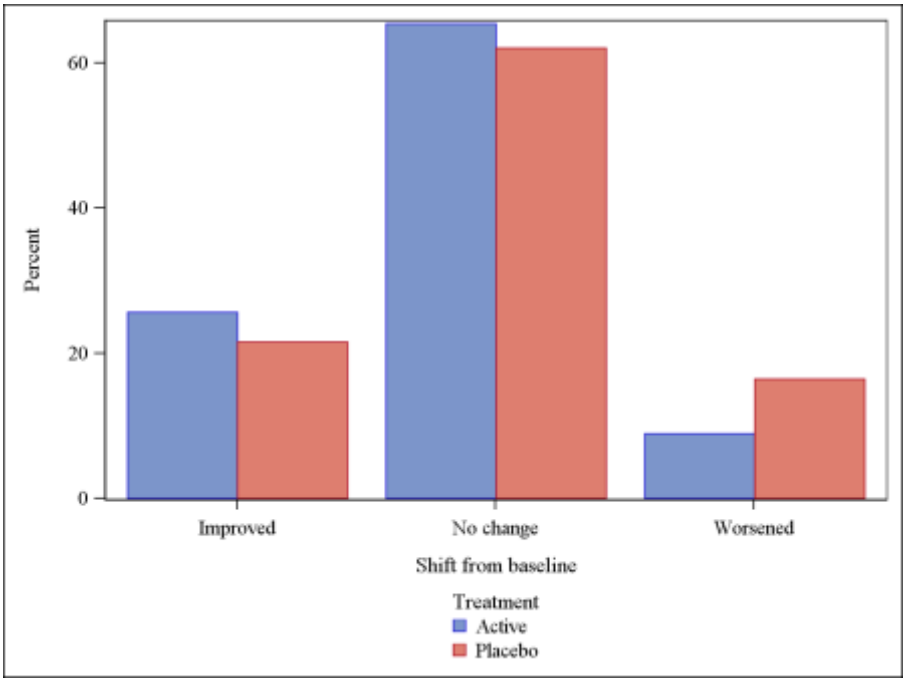


Figure 14.4 Rhinorrhea Symptom Score median change from baseline to Week 4, FAS

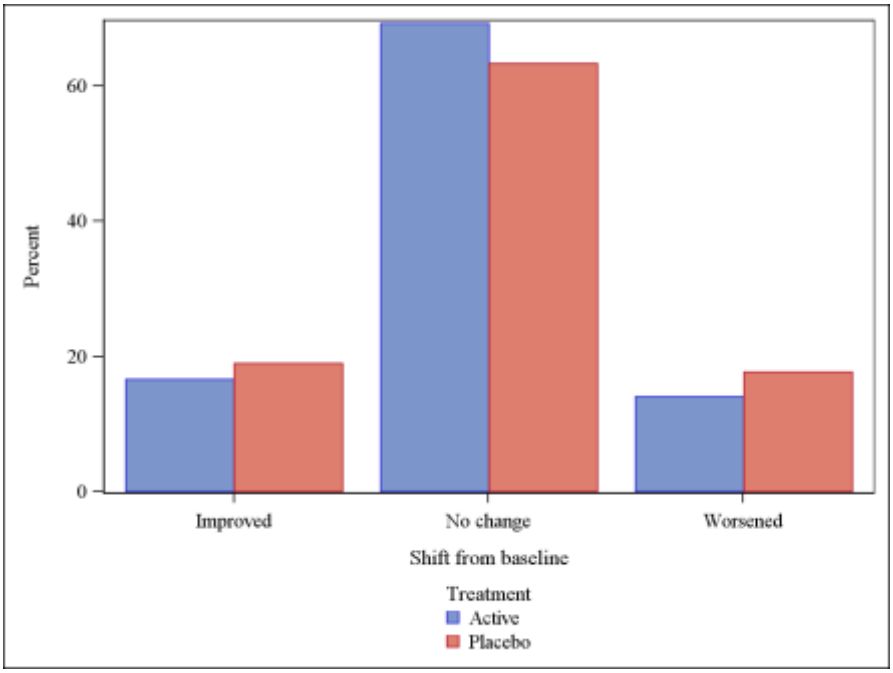


Figure 14.5 Postnasal Drip Symptom Score median change from baseline to Week 4, FAS

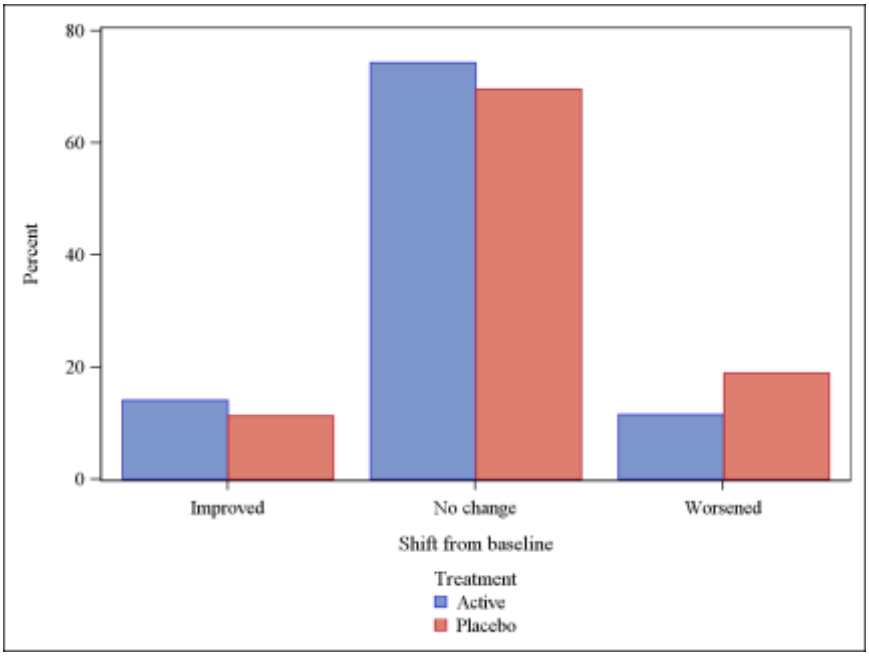


Figure 14.6 Sneezing Symptom Score median change from baseline to Week 4, FAS

Table 14.32 Weekly median individual symptom score by week up to Week 4, FAS (before and after first interim analysis)

			Old Active N=49		Low amplitude control N=47		New Active N=32		Placebo N=79	
Parameter	**Week**	**Score**	**n (%)**	**95% CI***	**n (%)**	**95% CI***	**n (%)**	**95% CI***	**n (%)**	**95% CI***
Nasal Congestion Symptom Score median	Week -1	None	0	(0.0%, 7.3%)	0	(0.0%, 7.5%)	0	(0.0%, 10.9%)	0	(0.0%, 4.6%)
		Mild	7 (14.3%)	(5.9%, 27.2%)	5 (10.6%)	(3.5%, 23.1%)	5 (15.6%)	(5.3%, 32.8%)	15 (19.0%)	(11.0%, 29.4%)
		Moderate	33 (67.3%)	(52.5%, 80.1%)	35 (74.5%)	(59.7%, 86.1%)	20 (62.5%)	(43.7%, 78.9%)	47 (59.5%)	(47.9%, 70.4%)
		Severe	9 (18.4%)	(8.8%, 32.0%)	7 (14.9%)	(6.2%, 28.3%)	7 (21.9%)	(9.3%, 40.0%)	17 (21.5%)	(13.1%, 32.2%)
	Week 1	None	2 (4.1%)	(0.5%, 14.0%)	4 (8.5%)	(2.4%, 20.4%)	0	(0.0%, 10.9%)	2 (2.5%)	(0.3%, 8.8%)
		Mild	15 (30.6%)	(18.3%, 45.4%)	12 (25.5%)	(13.9%, 40.3%)	10 (31.3%)	(16.1%, 50.0%)	23 (29.1%)	(19.4%, 40.4%)
		Moderate	28 (57.1%)	(42.2%, 71.2%)	29 (61.7%)	(46.4%, 75.5%)	18 (56.3%)	(37.7%, 73.6%)	42 (53.2%)	(41.6%, 64.5%)
		Severe	4 (8.2%)	(2.3%, 19.6%)	2 (4.3%)	(0.5%, 14.5%)	4 (12.5%)	(3.5%, 29.0%)	12 (15.2%)	(8.1%, 25.0%)
	Week 2	None	2 (4.1%)	(0.5%, 14.0%)	1 (2.2%)	(0.1%, 11.5%)	1 (3.1%)	(0.1%, 16.2%)	2 (2.5%)	(0.3%, 8.8%)
		Mild	19 (38.8%)	(25.2%, 53.8%)	15 (32.6%)	(19.5%, 48.0%)	14 (43.8%)	(26.4%, 62.3%)	23 (29.1%)	(19.4%, 40.4%)
		Moderate	23 (46.9%)	(32.5%, 61.7%)	28 (60.9%)	(45.4%, 74.9%)	14 (43.8%)	(26.4%, 62.3%)	43 (54.4%)	(42.8%, 65.7%)
		Severe	5 (10.2%)	(3.4%, 22.2%)	2 (4.3%)	(0.5%, 14.8%)	3 (9.4%)	(2.0%, 25.0%)	11 (13.9%)	(7.2%, 23.5%)
	Week 3	None	2 (4.2%)	(0.5%, 14.3%)	2 (4.4%)	(0.5%, 15.1%)	2 (6.3%)	(0.8%, 20.8%)	2 (2.5%)	(0.3%, 8.8%)
		Mild	19 (39.6%)	(25.8%, 54.7%)	17 (37.8%)	(23.8%, 53.5%)	12 (37.5%)	(21.1%, 56.3%)	22 (27.8%)	(18.3%, 39.1%)
		Moderate	21 (43.8%)	(29.5%, 58.8%)	22 (48.9%)	(33.7%, 64.2%)	12 (37.5%)	(21.1%, 56.3%)	43 (54.4%)	(42.8%, 65.7%)
		Severe	6 (12.5%)	(4.7%, 25.2%)	4 (8.9%)	(2.5%, 21.2%)	6 (18.8%)	(7.2%, 36.4%)	12 (15.2%)	(8.1%, 25.0%)
	Week 4	None	2 (4.3%)	(0.5%, 14.8%)	2 (4.4%)	(0.5%, 15.1%)	2 (6.3%)	(0.8%, 20.8%)	3 (3.8%)	(0.8%, 10.7%)
		Mild	17 (37.0%)	(23.2%, 52.5%)	19 (42.2%)	(27.7%, 57.8%)	10 (31.3%)	(16.1%, 50.0%)	17 (21.5%)	(13.1%, 32.2%)
		Moderate	26 (56.5%)	(41.1%, 71.1%)	21 (46.7%)	(31.7%, 62.1%)	16 (50.0%)	(31.9%, 68.1%)	48 (60.8%)	(49.1%, 71.6%)
		Severe	1 (2.2%)	(0.1%, 11.5%)	3 (6.7%)	(1.4%, 18.3%)	4 (12.5%)	(3.5%, 29.0%)	11 (13.9%)	(7.2%, 23.5%)
Rhinorrhea Symptom Score median	Week -1	None	19 (38.8%)	(25.2%, 53.8%)	17 (36.2%)	(22.7%, 51.5%)	14 (43.8%)	(26.4%, 62.3%)	39 (49.4%)	(37.9%, 60.9%)
		Mild	26 (53.1%)	(38.3%, 67.5%)	20 (42.6%)	(28.3%, 57.8%)	12 (37.5%)	(21.1%, 56.3%)	21 (26.6%)	(17.3%, 37.7%)
		Moderate	3 (6.1%)	(1.3%, 16.9%)	10 (21.3%)	(10.7%, 35.7%)	6 (18.8%)	(7.2%, 36.4%)	18 (22.8%)	(14.1%, 33.6%)
		Severe	1 (2.0%)	(0.1%, 10.9%)	0	(0.0%, 7.5%)	0	(0.0%, 10.9%)	1 (1.3%)	(0.0%, 6.9%)
	Week 1	None	19 (38.8%)	(25.2%, 53.8%)	21 (44.7%)	(30.2%, 59.9%)	18 (56.3%)	(37.7%, 73.6%)	32 (40.5%)	(29.6%, 52.1%)
		Mild	26 (53.1%)	(38.3%, 67.5%)	21 (44.7%)	(30.2%, 59.9%)	10 (31.3%)	(16.1%, 50.0%)	35 (44.3%)	(33.1%, 55.9%)
		Moderate	3 (6.1%)	(1.3%, 16.9%)	4 (8.5%)	(2.4%, 20.4%)	4 (12.5%)	(3.5%, 29.0%)	12 (15.2%)	(8.1%, 25.0%)

			Old Active N=49		Low amplitude control N=47		New Active N=32		Placebo N=79	
Parameter	**Week**	**Score**	**n (%)**	**95% CI***	**n (%)**	**95% CI***	**n (%)**	**95% CI***	**n (%)**	**95% CI***
		Severe	1 (2.0%)	(0.1%, 10.9%)	1 (2.1%)	(0.1%, 11.3%)	0	(0.0%, 10.9%)	0	(0.0%, 4.6%)
	Week 2	None	27 (55.1%)	(40.2%, 69.3%)	24 (52.2%)	(36.9%, 67.1%)	18 (56.3%)	(37.7%, 73.6%)	37 (46.8%)	(35.5%, 58.4%)
		Mild	17 (34.7%)	(21.7%, 49.6%)	16 (34.8%)	(21.4%, 50.2%)	8 (25.0%)	(11.5%, 43.4%)	28 (35.4%)	(25.0%, 47.0%)
		Moderate	4 (8.2%)	(2.3%, 19.6%)	6 (13.0%)	(4.9%, 26.3%)	6 (18.8%)	(7.2%, 36.4%)	11 (13.9%)	(7.2%, 23.5%)
		Severe	1 (2.0%)	(0.1%, 10.9%)	0	(0.0%, 7.7%)	0	(0.0%, 10.9%)	3 (3.8%)	(0.8%, 10.7%)
	Week 3	None	26 (54.2%)	(39.2%, 68.6%)	26 (57.8%)	(42.2%, 72.3%)	17 (53.1%)	(34.7%, 70.9%)	36 (45.6%)	(34.3%, 57.2%)
		Mild	15 (31.3%)	(18.7%, 46.3%)	14 (31.1%)	(18.2%, 46.6%)	11 (34.4%)	(18.6%, 53.2%)	29 (36.7%)	(26.1%, 48.3%)
		Moderate	6 (12.5%)	(4.7%, 25.2%)	5 (11.1%)	(3.7%, 24.1%)	4 (12.5%)	(3.5%, 29.0%)	13 (16.5%)	(9.1%, 26.5%)
		Severe	1 (2.1%)	(0.1%, 11.1%)	0	(0.0%, 7.9%)	0	(0.0%, 10.9%)	1 (1.3%)	(0.0%, 6.9%)
	Week 4	None	22 (47.8%)	(32.9%, 63.1%)	26 (57.8%)	(42.2%, 72.3%)	18 (56.3%)	(37.7%, 73.6%)	38 (48.1%)	(36.7%, 59.6%)
		Mild	21 (45.7%)	(30.9%, 61.0%)	15 (33.3%)	(20.0%, 49.0%)	13 (40.6%)	(23.7%, 59.4%)	31 (39.2%)	(28.4%, 50.9%)
		Moderate	3 (6.5%)	(1.4%, 17.9%)	4 (8.9%)	(2.5%, 21.2%)	1 (3.1%)	(0.1%, 16.2%)	7 (8.9%)	(3.6%, 17.4%)
		Severe	0	(0.0%, 7.7%)	0	(0.0%, 7.9%)	0	(0.0%, 10.9%)	3 (3.8%)	(0.8%, 10.7%)
Postnasal Drip Symptom Score median	Week -1	None	26 (53.1%)	(38.3%, 67.5%)	22 (46.8%)	(32.1%, 61.9%)	10 (31.3%)	(16.1%, 50.0%)	33 (41.8%)	(30.8%, 53.4%)
		Mild	14 (28.6%)	(16.6%, 43.3%)	11 (23.4%)	(12.3%, 38.0%)	15 (46.9%)	(29.1%, 65.3%)	35 (44.3%)	(33.1%, 55.9%)
		Moderate	7 (14.3%)	(5.9%, 27.2%)	12 (25.5%)	(13.9%, 40.3%)	7 (21.9%)	(9.3%, 40.0%)	11 (13.9%)	(7.2%, 23.5%)
		Severe	2 (4.1%)	(0.5%, 14.0%)	2 (4.3%)	(0.5%, 14.5%)	0	(0.0%, 10.9%)	0	(0.0%, 4.6%)
	Week 1	None	25 (51.0%)	(36.3%, 65.6%)	20 (42.6%)	(28.3%, 57.8%)	14 (43.8%)	(26.4%, 62.3%)	36 (45.6%)	(34.3%, 57.2%)
		Mild	13 (26.5%)	(14.9%, 41.1%)	14 (29.8%)	(17.3%, 44.9%)	12 (37.5%)	(21.1%, 56.3%)	29 (36.7%)	(26.1%, 48.3%)
		Moderate	9 (18.4%)	(8.8%, 32.0%)	12 (25.5%)	(13.9%, 40.3%)	5 (15.6%)	(5.3%, 32.8%)	13 (16.5%)	(9.1%, 26.5%)
		Severe	2 (4.1%)	(0.5%, 14.0%)	1 (2.1%)	(0.1%, 11.3%)	1 (3.1%)	(0.1%, 16.2%)	1 (1.3%)	(0.0%, 6.9%)
	Week 2	None	27 (55.1%)	(40.2%, 69.3%)	22 (47.8%)	(32.9%, 63.1%)	12 (37.5%)	(21.1%, 56.3%)	35 (44.3%)	(33.1%, 55.9%)
		Mild	15 (30.6%)	(18.3%, 45.4%)	11 (23.9%)	(12.6%, 38.8%)	15 (46.9%)	(29.1%, 65.3%)	28 (35.4%)	(25.0%, 47.0%)
		Moderate	6 (12.2%)	(4.6%, 24.8%)	12 (26.1%)	(14.3%, 41.1%)	4 (12.5%)	(3.5%, 29.0%)	15 (19.0%)	(11.0%, 29.4%)
		Severe	1 (2.0%)	(0.1%, 10.9%)	1 (2.2%)	(0.1%, 11.5%)	1 (3.1%)	(0.1%, 16.2%)	1 (1.3%)	(0.0%, 6.9%)
	Week 3	None	23 (47.9%)	(33.3%, 62.8%)	24 (53.3%)	(37.9%, 68.3%)	12 (37.5%)	(21.1%, 56.3%)	39 (49.4%)	(37.9%, 60.9%)
		Mild	19 (39.6%)	(25.8%, 54.7%)	11 (24.4%)	(12.9%, 39.5%)	12 (37.5%)	(21.1%, 56.3%)	27 (34.2%)	(23.9%, 45.7%)
		Moderate	6 (12.5%)	(4.7%, 25.2%)	9 (20.0%)	(9.6%, 34.6%)	6 (18.8%)	(7.2%, 36.4%)	11 (13.9%)	(7.2%, 23.5%)
		Severe	0	(0.0%, 7.4%)	1 (2.2%)	(0.1%, 11.8%)	2 (6.3%)	(0.8%, 20.8%)	2 (2.5%)	(0.3%, 8.8%)

			Old Active N=49		Low amplitude control N=47		New Active N=32		Placebo N=79	
Parameter	**Week**	**Score**	**n (%)**	**95% CI***	**n (%)**	**95% CI***	**n (%)**	**95% CI***	**n (%)**	**95% CI***
	Week 4	None	25 (54.3%)	(39.0%, 69.1%)	24 (53.3%)	(37.9%, 68.3%)	9 (28.1%)	(13.7%, 46.7%)	39 (49.4%)	(37.9%, 60.9%)
		Mild	17 (37.0%)	(23.2%, 52.5%)	12 (26.7%)	(14.6%, 41.9%)	16 (50.0%)	(31.9%, 68.1%)	24 (30.4%)	(20.5%, 41.8%)
		Moderate	2 (4.3%)	(0.5%, 14.8%)	8 (17.8%)	(8.0%, 32.1%)	6 (18.8%)	(7.2%, 36.4%)	15 (19.0%)	(11.0%, 29.4%)
		Severe	2 (4.3%)	(0.5%, 14.8%)	1 (2.2%)	(0.1%, 11.8%)	1 (3.1%)	(0.1%, 16.2%)	1 (1.3%)	(0.0%, 6.9%)
Sneezing Symptom Score median	Week -1	None	33 (67.3%)	(52.5%, 80.1%)	31 (66.0%)	(50.7%, 79.1%)	17 (53.1%)	(34.7%, 70.9%)	58 (73.4%)	(62.3%, 82.7%)
		Mild	13 (26.5%)	(14.9%, 41.1%)	13 (27.7%)	(15.6%, 42.6%)	11 (34.4%)	(18.6%, 53.2%)	20 (25.3%)	(16.2%, 36.4%)
		Moderate	3 (6.1%)	(1.3%, 16.9%)	3 (6.4%)	(1.3%, 17.5%)	4 (12.5%)	(3.5%, 29.0%)	1 (1.3%)	(0.0%, 6.9%)
		Severe	0	(0.0%, 7.3%)	0	(0.0%, 7.5%)	0	(0.0%, 10.9%)	0	(0.0%, 4.6%)
	Week 1	None	34 (69.4%)	(54.6%, 81.7%)	35 (74.5%)	(59.7%, 86.1%)	23 (71.9%)	(53.3%, 86.3%)	54 (68.4%)	(56.9%, 78.4%)
		Mild	13 (26.5%)	(14.9%, 41.1%)	10 (21.3%)	(10.7%, 35.7%)	8 (25.0%)	(11.5%, 43.4%)	23 (29.1%)	(19.4%, 40.4%)
		Moderate	2 (4.1%)	(0.5%, 14.0%)	2 (4.3%)	(0.5%, 14.5%)	1 (3.1%)	(0.1%, 16.2%)	2 (2.5%)	(0.3%, 8.8%)
		Severe	0	(0.0%, 7.3%)	0	(0.0%, 7.5%)	0	(0.0%, 10.9%)	0	(0.0%, 4.6%)
	Week 2	None	31 (63.3%)	(48.3%, 76.6%)	31 (67.4%)	(52.0%, 80.5%)	20 (62.5%)	(43.7%, 78.9%)	51 (64.6%)	(53.0%, 75.0%)
		Mild	16 (32.7%)	(19.9%, 47.5%)	14 (30.4%)	(17.7%, 45.8%)	10 (31.3%)	(16.1%, 50.0%)	24 (30.4%)	(20.5%, 41.8%)
		Moderate	2 (4.1%)	(0.5%, 14.0%)	1 (2.2%)	(0.1%, 11.5%)	2 (6.3%)	(0.8%, 20.8%)	3 (3.8%)	(0.8%, 10.7%)
		Severe	0	(0.0%, 7.3%)	0	(0.0%, 7.7%)	0	(0.0%, 10.9%)	1 (1.3%)	(0.0%, 6.9%)
	Week 3	None	35 (72.9%)	(58.2%, 84.7%)	32 (71.1%)	(55.7%, 83.6%)	19 (59.4%)	(40.6%, 76.3%)	58 (73.4%)	(62.3%, 82.7%)
		Mild	11 (22.9%)	(12.0%, 37.3%)	11 (24.4%)	(12.9%, 39.5%)	10 (31.3%)	(16.1%, 50.0%)	16 (20.3%)	(12.0%, 30.8%)
		Moderate	1 (2.1%)	(0.1%, 11.1%)	2 (4.4%)	(0.5%, 15.1%)	3 (9.4%)	(2.0%, 25.0%)	5 (6.3%)	(2.1%, 14.2%)
		Severe	1 (2.1%)	(0.1%, 11.1%)	0	(0.0%, 7.9%)	0	(0.0%, 10.9%)	0	(0.0%, 4.6%)
	Week 4	None	31 (67.4%)	(52.0%, 80.5%)	33 (73.3%)	(58.1%, 85.4%)	19 (59.4%)	(40.6%, 76.3%)	54 (68.4%)	(56.9%, 78.4%)
		Mild	10 (21.7%)	(10.9%, 36.4%)	10 (22.2%)	(11.2%, 37.1%)	11 (34.4%)	(18.6%, 53.2%)	21 (26.6%)	(17.3%, 37.7%)
		Moderate	5 (10.9%)	(3.6%, 23.6%)	2 (4.4%)	(0.5%, 15.1%)	2 (6.3%)	(0.8%, 20.8%)	3 (3.8%)	(0.8%, 10.7%)
		Severe	0	(0.0%, 7.7%)	0	(0.0%, 7.9%)	0	(0.0%, 10.9%)	1 (1.3%)	(0.0%, 6.9%)

*Confidence intervals calculated using Clopper-Pearson method.

Table 14.33 Change from baseline of Weekly median individual symptom score at Week 4, FAS (before and after first interim analysis)

Parameter	Week	Shift from baseline	Old Active N=49		Low amplitude control N=47		New Active N=32		Placebo N=79	
			n (%)	95% CI*	n (%)	95% CI*	n (%)	95% CI*	n (%)	95% CI*
Nasal Congestion Symptom Score median	Week 4	Improved	21 (45.7%)	(30.9%, 61.0%)	21 (46.7%)	(31.7%, 62.1%)	12 (37.5%)	(21.1%, 56.3%)	17 (21.5%)	(13.1%, 32.2%)
		No change	22 (47.8%)	(32.9%, 63.1%)	22 (48.9%)	(33.7%, 64.2%)	18 (56.3%)	(37.7%, 73.6%)	54 (68.4%)	(56.9%, 78.4%)
		Worsened	3 (6.5%)	(1.4%, 17.9%)	2 (4.4%)	(0.5%, 15.1%)	2 (6.3%)	(0.8%, 20.8%)	8 (10.1%)	(4.5%, 19.0%)
Postnasal Drip Symptom Score median	Week 4	Improved	9 (19.6%)	(9.4%, 33.9%)	13 (28.9%)	(16.4%, 44.3%)	4 (12.5%)	(3.5%, 29.0%)	15 (19.0%)	(11.0%, 29.4%)
		No change	32 (69.6%)	(54.2%, 82.3%)	26 (57.8%)	(42.2%, 72.3%)	22 (68.8%)	(50.0%, 83.9%)	50 (63.3%)	(51.7%, 73.9%)
		Worsened	5 (10.9%)	(3.6%, 23.6%)	6 (13.3%)	(5.1%, 26.8%)	6 (18.8%)	(7.2%, 36.4%)	14 (17.7%)	(10.0%, 27.9%)
Rhinorrhea Symptom Score median	Week 4	Improved	10 (21.7%)	(10.9%, 36.4%)	18 (40.0%)	(25.7%, 55.7%)	10 (31.3%)	(16.1%, 50.0%)	17 (21.5%)	(13.1%, 32.2%)
		No change	30 (65.2%)	(49.8%, 78.6%)	23 (51.1%)	(35.8%, 66.3%)	21 (65.6%)	(46.8%, 81.4%)	49 (62.0%)	(50.4%, 72.7%)
		Worsened	6 (13.0%)	(4.9%, 26.3%)	4 (8.9%)	(2.5%, 21.2%)	1 (3.1%)	(0.1%, 16.2%)	13 (16.5%)	(9.1%, 26.5%)
Sneezing Symptom Score median	Week 4	Improved	6 (13.0%)	(4.9%, 26.3%)	7 (15.6%)	(6.5%, 29.5%)	5 (15.6%)	(5.3%, 32.8%)	9 (11.4%)	(5.3%, 20.5%)
		No change	33 (71.7%)	(56.5%, 84.0%)	34 (75.6%)	(60.5%, 87.1%)	25 (78.1%)	(60.0%, 90.7%)	55 (69.6%)	(58.2%, 79.5%)
		Worsened	7 (15.2%)	(6.3%, 28.9%)	4 (8.9%)	(2.5%, 21.2%)	2 (6.3%)	(0.8%, 20.8%)	15 (19.0%)	(11.0%, 29.4%)

* Confidence intervals calculated using Clopper-Pearson method.

Table 14.34 Weekly median individual symptom score at Weeks 8, 12 and 24, FAS

Parameter	Week	Score	Active + Active N=81		Placebo + Active N=79	
			n (%)	95% CI*	n (%)	95% CI*
Nasal Congestion Symptom Score median	Week 8	None	9 (12.3%)	(5.8%, 22.1%)	7 (9.3%)	(3.8%, 18.3%)
		Mild	32 (43.8%)	(32.2%, 55.9%)	29 (38.7%)	(27.6%, 50.6%)
		Moderate	29 (39.7%)	(28.5%, 51.9%)	32 (42.7%)	(31.3%, 54.6%)
		Severe	3 (4.1%)	(0.9%, 11.5%)	7 (9.3%)	(3.8%, 18.3%)
	Week 12	None	7 (9.1%)	(3.7%, 17.8%)	4 (5.5%)	(1.5%, 13.4%)
		Mild	33 (42.9%)	(31.6%, 54.6%)	27 (37.0%)	(26.0%, 49.1%)
		Moderate	31 (40.3%)	(29.2%, 52.1%)	34 (46.6%)	(34.8%, 58.6%)
		Severe	6 (7.8%)	(2.9%, 16.2%)	8 (11.0%)	(4.9%, 20.5%)
	Week 24	None	9 (12.9%)	(6.1%, 23.0%)	11 (16.2%)	(8.4%, 27.1%)
		Mild	24 (34.3%)	(23.3%, 46.6%)	26 (38.2%)	(26.7%, 50.8%)
		Moderate	30 (42.9%)	(31.1%, 55.3%)	25 (36.8%)	(25.4%, 49.3%)
		Severe	7 (10.0%)	(4.1%, 19.5%)	6 (8.8%)	(3.3%, 18.2%)
Rhinorrhea Symptom Score median	Week 8	None	43 (58.9%)	(46.8%, 70.3%)	42 (56.0%)	(44.1%, 67.5%)
		Mild	27 (37.0%)	(26.0%, 49.1%)	23 (30.7%)	(20.5%, 42.4%)
		Moderate	3 (4.1%)	(0.9%, 11.5%)	9 (12.0%)	(5.6%, 21.6%)
		Severe	0	(0.0%, 4.9%)	1 (1.3%)	(0.0%, 7.2%)
	Week 12	None	48 (62.3%)	(50.6%, 73.1%)	41 (56.2%)	(44.1%, 67.8%)
		Mild	24 (31.2%)	(21.1%, 42.7%)	20 (27.4%)	(17.6%, 39.1%)
		Moderate	4 (5.2%)	(1.4%, 12.8%)	11 (15.1%)	(7.8%, 25.4%)
		Severe	1 (1.3%)	(0.0%, 7.0%)	1 (1.4%)	(0.0%, 7.4%)
	Week 24	None	40 (57.1%)	(44.7%, 68.9%)	46 (67.6%)	(55.2%, 78.5%)
		Mild	18 (25.7%)	(16.0%, 37.6%)	16 (23.5%)	(14.1%, 35.4%)
		Moderate	12 (17.1%)	(9.2%, 28.0%)	5 (7.4%)	(2.4%, 16.3%)
		Severe	0	(0.0%, 5.1%)	1 (1.5%)	(0.0%, 7.9%)
Postnasal Drip Symptom Score median	Week 8	None	40 (54.8%)	(42.7%, 66.5%)	30 (40.0%)	(28.9%, 52.0%)
		Mild	24 (32.9%)	(22.3%, 44.9%)	31 (41.3%)	(30.1%, 53.3%)
		Moderate	9 (12.3%)	(5.8%, 22.1%)	13 (17.3%)	(9.6%, 27.8%)
		Severe	0	(0.0%, 4.9%)	1 (1.3%)	(0.0%, 7.2%)
	Week 12	None	41 (53.2%)	(41.5%, 64.7%)	31 (42.5%)	(31.0%, 54.6%)
		Mild	22 (28.6%)	(18.8%, 40.0%)	29 (39.7%)	(28.5%, 51.9%)
		Moderate	12 (15.6%)	(8.3%, 25.6%)	11 (15.1%)	(7.8%, 25.4%)
		Severe	2 (2.6%)	(0.3%, 9.1%)	2 (2.7%)	(0.3%, 9.5%)
	Week 24	None	29 (41.4%)	(29.8%, 53.8%)	39 (57.4%)	(44.8%, 69.3%)
		Mild	28 (40.0%)	(28.5%, 52.4%)	21 (30.9%)	(20.2%, 43.3%)
		Moderate	13 (18.6%)	(10.3%, 29.7%)	7 (10.3%)	(4.2%, 20.1%)
		Severe	0	(0.0%, 5.1%)	1 (1.5%)	(0.0%, 7.9%)
Sneezing Symptom Score median	Week 8	None	52 (71.2%)	(59.4%, 81.2%)	52 (69.3%)	(57.6%, 79.5%)
		Mild	20 (27.4%)	(17.6%, 39.1%)	20 (26.7%)	(17.1%, 38.1%)
		Moderate	1 (1.4%)	(0.0%, 7.4%)	3 (4.0%)	(0.8%, 11.2%)
	Week 12	None	55 (71.4%)	(60.0%, 81.2%)	53 (72.6%)	(60.9%, 82.4%)
		Mild	20 (26.0%)	(16.6%, 37.2%)	16 (21.9%)	(13.1%, 33.1%)
		Moderate	2 (2.6%)	(0.3%, 9.1%)	4 (5.5%)	(1.5%, 13.4%)
	Week 24	None	45 (64.3%)	(51.9%, 75.4%)	48 (70.6%)	(58.3%, 81.0%)
		Mild	22 (31.4%)	(20.9%, 43.6%)	18 (26.5%)	(16.5%, 38.6%)
		Moderate	3 (4.3%)	(0.9%, 12.0%)	2 (2.9%)	(0.4%, 10.2%)

*Confidence intervals calculated using Clopper-Pearson method.

Table 14.35 Shift from baseline to Weeks 8, 12 and 24 in weekly median individual symptom scores, FAS

			Active + Active N=81					Placebo + Active N=79				
			Baseline					Baseline				
	Week	Post-baseline	None	Mild	Moderate	Severe	Total	None	Mild	Moderate	Severe	Total
Nasal Congestion Symptom Score	8	None	0	3 (4.1%)	5 (6.8%)	1 (1.4%)	9 (12.3%)	0	3 (4.0%)	3 (4.0%)	1 (1.3%)	7 (9.3%)
		Mild	0	8 (11.0%)	20 (27.4%)	4 (5.5%)	32 (43.8%)	0	11 (14.7%)	17 (22.7%)	1 (1.3%)	29 (38.7%)
		Moderate	0	1 (1.4%)	21 (28.8%)	7 (9.6%)	29 (39.7%)	0	1 (1.3%)	22 (29.3%)	9 (12.0%)	32 (42.7%)
		Severe	0	0	1 (1.4%)	2 (2.7%)	3 (4.1%)	0	0	2 (2.7%)	5 (6.7%)	7 (9.3%)
		Total	0	12 (16.4%)	47 (64.4%)	14 (19.2%)	73 (100.0%)	0	15 (20.0%)	44 (58.7%)	16 (21.3%)	75 (100.0%)
	12	None	0	1 (1.3%)	6 (7.8%)	0	7 (9.1%)	0	3 (4.1%)	0	1 (1.4%)	4 (5.5%)
		Mild	0	9 (11.7%)	20 (26.0%)	4 (5.2%)	33 (42.9%)	0	8 (11.0%)	14 (19.2%)	5 (6.8%)	27 (37.0%)
		Moderate	0	2 (2.6%)	23 (29.9%)	6 (7.8%)	31 (40.3%)	0	4 (5.5%)	25 (34.2%)	5 (6.8%)	34 (46.6%)
		Severe	0	0	2 (2.6%)	4 (5.2%)	6 (7.8%)	0	0	4 (5.5%)	4 (5.5%)	8 (11.0%)
		Total	0	12 (15.6%)	51 (66.2%)	14 (18.2%)	77 (100.0%)	0	15 (20.5%)	43 (58.9%)	15 (20.5%)	73 (100.0%)
	24	None	0	1 (1.4%)	7 (10.0%)	1 (1.4%)	9 (12.9%)	0	5 (7.4%)	5 (7.4%)	1 (1.5%)	11 (16.2%)
		Mild	0	5 (7.1%)	17 (24.3%)	2 (2.9%)	24 (34.3%)	0	6 (8.8%)	16 (23.5%)	4 (5.9%)	26 (38.2%)
		Moderate	0	4 (5.7%)	20 (28.6%)	6 (8.6%)	30 (42.9%)	0	4 (5.9%)	16 (23.5%)	5 (7.4%)	25 (36.8%)
		Severe	0	1 (1.4%)	3 (4.3%)	3 (4.3%)	7 (10.0%)	0	0	3 (4.4%)	3 (4.4%)	6 (8.8%)
		Total	0	11 (15.7%)	47 (67.1%)	12 (17.1%)	70 (100.0%)	0	15 (22.1%)	40 (58.8%)	13 (19.1%)	68 (100.0%)
Postnasal Drip Symptom Score	8	None	24 (32.9%)	17 (23.3%)	2 (2.7%)	0	43 (58.9%)	29 (38.7%)	11 (14.7%)	2 (2.7%)	0	42 (56.0%)
		Mild	6 (8.2%)	14 (19.2%)	6 (8.2%)	1 (1.4%)	27 (37.0%)	6 (8.0%)	8 (10.7%)	9 (12.0%)	0	23 (30.7%)
		Moderate	0	2 (2.7%)	1 (1.4%)	0	3 (4.1%)	1 (1.3%)	2 (2.7%)	5 (6.7%)	1 (1.3%)	9 (12.0%)
		Severe	0	0	0	0	0	0	0	1 (1.3%)	0	1 (1.3%)
		Total	30 (41.1%)	33 (45.2%)	9 (12.3%)	1 (1.4%)	73 (100.0%)	36 (48.0%)	21 (28.0%)	17 (22.7%)	1 (1.3%)	75 (100.0%)
	12	None	29 (37.7%)	15 (19.5%)	4 (5.2%)	0	48 (62.3%)	27 (37.0%)	11 (15.1%)	3 (4.1%)	0	41 (56.2%)
		Mild	3 (3.9%)	17 (22.1%)	3 (3.9%)	1 (1.3%)	24 (31.2%)	5 (6.8%)	8 (11.0%)	7 (9.6%)	0	20 (27.4%)
		Moderate	0	3 (3.9%)	1 (1.3%)	0	4 (5.2%)	2 (2.7%)	2 (2.7%)	7 (9.6%)	0	11 (15.1%)
		Severe	0	0	1 (1.3%)	0	1 (1.3%)	0	0	0	1 (1.4%)	1 (1.4%)
		Total	32 (41.6%)	35 (45.5%)	9 (11.7%)	1 (1.3%)	77 (100.0%)	34 (46.6%)	21 (28.8%)	17 (23.3%)	1 (1.4%)	73 (100.0%)
	24	None	22 (31.4%)	17 (24.3%)	1 (1.4%)	0	40 (57.1%)	32 (47.1%)	11 (16.2%)	3 (4.4%)	0	46 (67.6%)

	Week	Post-baseline	Active + Active N=81					Placebo + Active N=79				
			Baseline					Baseline				
			None	Mild	Moderate	Severe	Total	None	Mild	Moderate	Severe	Total
		Mild	5 (7.1%)	10 (14.3%)	3 (4.3%)	0	18 (25.7%)	1 (1.5%)	8 (11.8%)	7 (10.3%)	0	16 (23.5%)
		Moderate	1 (1.4%)	6 (8.6%)	4 (5.7%)	1 (1.4%)	12 (17.1%)	0	0	4 (5.9%)	1 (1.5%)	5 (7.4%)
		Severe	0	0	0	0	0	0	1 (1.5%)	0	0	1 (1.5%)
		Total	28 (40.0%)	33 (47.1%)	8 (11.4%)	1 (1.4%)	70 (100.0%)	33 (48.5%)	20 (29.4%)	14 (20.6%)	1 (1.5%)	68 (100.0%)
Rhinorrhea Symptom Score	8	None	25 (34.2%)	13 (17.8%)	1 (1.4%)	1 (1.4%)	40 (54.8%)	22 (29.3%)	7 (9.3%)	1 (1.3%)	0	30 (40.0%)
		Mild	4 (5.5%)	16 (21.9%)	4 (5.5%)	0	24 (32.9%)	5 (6.7%)	21 (28.0%)	5 (6.7%)	0	31 (41.3%)
		Moderate	0	0	8 (11.0%)	1 (1.4%)	9 (12.3%)	3 (4.0%)	5 (6.7%)	5 (6.7%)	0	13 (17.3%)
		Severe	0	0	0	0	0	0	1 (1.3%)	0	0	1 (1.3%)
		Total	29 (39.7%)	29 (39.7%)	13 (17.8%)	2 (2.7%)	73 (100.0%)	30 (40.0%)	34 (45.3%)	11 (14.7%)	0	75 (100.0%)
	12	None	28 (36.4%)	12 (15.6%)	1 (1.3%)	0	41 (53.2%)	21 (28.8%)	9 (12.3%)	1 (1.4%)	0	31 (42.5%)
		Mild	5 (6.5%)	14 (18.2%)	3 (3.9%)	0	22 (28.6%)	5 (6.8%)	18 (24.7%)	6 (8.2%)	0	29 (39.7%)
		Moderate	0	2 (2.6%)	8 (10.4%)	2 (2.6%)	12 (15.6%)	4 (5.5%)	5 (6.8%)	2 (2.7%)	0	11 (15.1%)
		Severe	0	0	2 (2.6%)	0	2 (2.6%)	0	1 (1.4%)	1 (1.4%)	0	2 (2.7%)
		Total	33 (42.9%)	28 (36.4%)	14 (18.2%)	2 (2.6%)	77 (100.0%)	30 (41.1%)	33 (45.2%)	10 (13.7%)	0	73 (100.0%)
	24	None	19 (27.1%)	9 (12.9%)	1 (1.4%)	0	29 (41.4%)	24 (35.3%)	14 (20.6%)	1 (1.5%)	0	39 (57.4%)
		Mild	8 (11.4%)	15 (21.4%)	4 (5.7%)	1 (1.4%)	28 (40.0%)	3 (4.4%)	13 (19.1%)	5 (7.4%)	0	21 (30.9%)
		Moderate	1 (1.4%)	3 (4.3%)	8 (11.4%)	1 (1.4%)	13 (18.6%)	1 (1.5%)	2 (2.9%)	4 (5.9%)	0	7 (10.3%)
		Severe	0	0	0	0	0	0	1 (1.5%)	0	0	1 (1.5%)
		Total	28 (40.0%)	27 (38.6%)	13 (18.6%)	2 (2.9%)	70 (100.0%)	28 (41.2%)	30 (44.1%)	10 (14.7%)	0	68 (100.0%)
Sneezing Symptom Score	8	None	39 (53.4%)	12 (16.4%)	1 (1.4%)	0	52 (71.2%)	42 (56.0%)	10 (13.3%)	0	0	52 (69.3%)
		Mild	4 (5.5%)	11 (15.1%)	5 (6.8%)	0	20 (27.4%)	11 (14.7%)	9 (12.0%)	0	0	20 (26.7%)
		Moderate	0	0	1 (1.4%)	0	1 (1.4%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	0	3 (4.0%)
		Severe	0	0	0	0	0	0	0	0	0	0
		Total	43 (58.9%)	23 (31.5%)	7 (9.6%)	0	73 (100.0%)	54 (72.0%)	20 (26.7%)	1 (1.3%)	0	75 (100.0%)
	12	None	43 (55.8%)	10 (13.0%)	2 (2.6%)	0	55 (71.4%)	41 (56.2%)	12 (16.4%)	0	0	53 (72.6%)
		Mild	4 (5.2%)	12 (15.6%)	4 (5.2%)	0	20 (26.0%)	11 (15.1%)	5 (6.8%)	0	0	16 (21.9%)
		Moderate	0	1 (1.3%)	1 (1.3%)	0	2 (2.6%)	0	3 (4.1%)	1 (1.4%)	0	4 (5.5%)
		Severe	0	0	0	0	0	0	0	0	0	0

Week	Post-baseline	Active + Active N=81					Placebo + Active N=79				
		Baseline					Baseline				
		None	Mild	Moderate	Severe	Total	None	Mild	Moderate	Severe	Total
	Total	47 (61.0%)	23 (29.9%)	7 (9.1%)	0	77 (100.0%)	52 (71.2%)	20 (27.4%)	1 (1.4%)	0	73 (100.0%)
24	None	37 (52.9%)	8 (11.4%)	0	0	45 (64.3%)	40 (58.8%)	8 (11.8%)	0	0	48 (70.6%)
	Mild	5 (7.1%)	14 (20.0%)	3 (4.3%)	0	22 (31.4%)	11 (16.2%)	7 (10.3%)	0	0	18 (26.5%)
	Moderate	0	0	3 (4.3%)	0	3 (4.3%)	0	2 (2.9%)	0	0	2 (2.9%)
	Severe	0	0	0	0	0	0	0	0	0	0
	Total	42 (60.0%)	22 (31.4%)	6 (8.6%)	0	70 (100.0%)	51 (75.0%)	17 (25.0%)	0	0	68 (100.0%)

Percentages are based on the number of subjects with a non-missing value before and after treatment within each treatment group.

Table 14.36 Weekly median individual symptom score at Weeks 8, 12 and 24, FAS (before and after first interim analysis)

			Old Active + Active N=49		Low amplitude control + Active N=47		New Active + Active N=32		Placebo + Active N=79	
Parameter	Visit	Score	n (%)	95% CI*	n (%)	95% CI*	n (%)	95% CI*	n (%)	95% CI*
Nasal Congestion Symptom Score median	Week 8	None	5 (11.9%)	(4.0%, 25.6%)	0	(0.0%, 8.4%)	4 (12.9%)	(3.6%, 29.8%)	7 (9.3%)	(3.8%, 18.3%)
		Mild	20 (47.6%)	(32.0%, 63.6%)	22 (52.4%)	(36.4%, 68.0%)	12 (38.7%)	(21.8%, 57.8%)	29 (38.7%)	(27.6%, 50.6%)
		Moderate	17 (40.5%)	(25.6%, 56.7%)	17 (40.5%)	(25.6%, 56.7%)	12 (38.7%)	(21.8%, 57.8%)	32 (42.7%)	(31.3%, 54.6%)
		Severe	0	(0.0%, 8.4%)	3 (7.1%)	(1.5%, 19.5%)	3 (9.7%)	(2.0%, 25.8%)	7 (9.3%)	(3.8%, 18.3%)
	Week 12	None	4 (8.7%)	(2.4%, 20.8%)	1 (2.4%)	(0.1%, 12.6%)	3 (9.7%)	(2.0%, 25.8%)	4 (5.5%)	(1.5%, 13.4%)
		Mild	20 (43.5%)	(28.9%, 58.9%)	23 (54.8%)	(38.7%, 70.2%)	13 (41.9%)	(24.5%, 60.9%)	27 (37.0%)	(26.0%, 49.1%)
		Moderate	20 (43.5%)	(28.9%, 58.9%)	14 (33.3%)	(19.6%, 49.5%)	11 (35.5%)	(19.2%, 54.6%)	34 (46.6%)	(34.8%, 58.6%)
		Severe	2 (4.3%)	(0.5%, 14.8%)	4 (9.5%)	(2.7%, 22.6%)	4 (12.9%)	(3.6%, 29.8%)	8 (11.0%)	(4.9%, 20.5%)
	Week 24	None	3 (7.0%)	(1.5%, 19.1%)	3 (7.5%)	(1.6%, 20.4%)	6 (22.2%)	(8.6%, 42.3%)	11 (16.2%)	(8.4%, 27.1%)
		Mild	13 (30.2%)	(17.2%, 46.1%)	15 (37.5%)	(22.7%, 54.2%)	11 (40.7%)	(22.4%, 61.2%)	26 (38.2%)	(26.7%, 50.8%)
		Moderate	24 (55.8%)	(39.9%, 70.9%)	19 (47.5%)	(31.5%, 63.9%)	6 (22.2%)	(8.6%, 42.3%)	25 (36.8%)	(25.4%, 49.3%)
		Severe	3 (7.0%)	(1.5%, 19.1%)	3 (7.5%)	(1.6%, 20.4%)	4 (14.8%)	(4.2%, 33.7%)	6 (8.8%)	(3.3%, 18.2%)
Rhinorrhea Symptom Score median	Week 8	None	27 (64.3%)	(48.0%, 78.4%)	28 (66.7%)	(50.5%, 80.4%)	16 (51.6%)	(33.1%, 69.8%)	42 (56.0%)	(44.1%, 67.5%)
		Mild	13 (31.0%)	(17.6%, 47.1%)	9 (21.4%)	(10.3%, 36.8%)	14 (45.2%)	(27.3%, 64.0%)	23 (30.7%)	(20.5%, 42.4%)
		Moderate	2 (4.8%)	(0.6%, 16.2%)	5 (11.9%)	(4.0%, 25.6%)	1 (3.2%)	(0.1%, 16.7%)	9 (12.0%)	(5.6%, 21.6%)
		Severe	0	(0.0%, 8.4%)	0	(0.0%, 8.4%)	0	(0.0%, 11.2%)	1 (1.3%)	(0.0%, 7.2%)
	Week 12	None	29 (63.0%)	(47.5%, 76.8%)	28 (66.7%)	(50.5%, 80.4%)	19 (61.3%)	(42.2%, 78.2%)	41 (56.2%)	(44.1%, 67.8%)
		Mild	14 (30.4%)	(17.7%, 45.8%)	9 (21.4%)	(10.3%, 36.8%)	10 (32.3%)	(16.7%, 51.4%)	20 (27.4%)	(17.6%, 39.1%)
		Moderate	3 (6.5%)	(1.4%, 17.9%)	3 (7.1%)	(1.5%, 19.5%)	1 (3.2%)	(0.1%, 16.7%)	11 (15.1%)	(7.8%, 25.4%)
		Severe	0	(0.0%, 7.7%)	2 (4.8%)	(0.6%, 16.2%)	1 (3.2%)	(0.1%, 16.7%)	1 (1.4%)	(0.0%, 7.4%)
	Week 24	None	23 (53.5%)	(37.7%, 68.8%)	24 (60.0%)	(43.3%, 75.1%)	17 (63.0%)	(42.4%, 80.6%)	46 (67.6%)	(55.2%, 78.5%)
		Mild	12 (27.9%)	(15.3%, 43.7%)	12 (30.0%)	(16.6%, 46.5%)	6 (22.2%)	(8.6%, 42.3%)	16 (23.5%)	(14.1%, 35.4%)
		Moderate	8 (18.6%)	(8.4%, 33.4%)	2 (5.0%)	(0.6%, 16.9%)	4 (14.8%)	(4.2%, 33.7%)	5 (7.4%)	(2.4%, 16.3%)
		Severe	0	(0.0%, 8.2%)	2 (5.0%)	(0.6%, 16.9%)	0	(0.0%, 12.8%)	1 (1.5%)	(0.0%, 7.9%)
Postnasal Drip Symptom Score median	Week 8	None	26 (61.9%)	(45.6%, 76.4%)	23 (54.8%)	(38.7%, 70.2%)	14 (45.2%)	(27.3%, 64.0%)	30 (40.0%)	(28.9%, 52.0%)
		Mild	11 (26.2%)	(13.9%, 42.0%)	14 (33.3%)	(19.6%, 49.5%)	13 (41.9%)	(24.5%, 60.9%)	31 (41.3%)	(30.1%, 53.3%)
		Moderate	5 (11.9%)	(4.0%, 25.6%)	5 (11.9%)	(4.0%, 25.6%)	4 (12.9%)	(3.6%, 29.8%)	13 (17.3%)	(9.6%, 27.8%)
		Severe	0	(0.0%, 8.4%)	0	(0.0%, 8.4%)	0	(0.0%, 11.2%)	1 (1.3%)	(0.0%, 7.2%)
	Week 12	None	27 (58.7%)	(43.2%, 73.0%)	23 (54.8%)	(38.7%, 70.2%)	14 (45.2%)	(27.3%, 64.0%)	31 (42.5%)	(31.0%, 54.6%)
		Mild	10 (21.7%)	(10.9%, 36.4%)	14 (33.3%)	(19.6%, 49.5%)	12 (38.7%)	(21.8%, 57.8%)	29 (39.7%)	(28.5%, 51.9%)

Parameter	Visit	Score	Old Active + Active N=49		Low amplitude control + Active N=47		New Active + Active N=32		Placebo + Active N=79	
			n (%)	95% CI*	n (%)	95% CI*	n (%)	95% CI*	n (%)	95% CI*
		Moderate	8 (17.4%)	(7.8%, 31.4%)	5 (11.9%)	(4.0%, 25.6%)	4 (12.9%)	(3.6%, 29.8%)	11 (15.1%)	(7.8%, 25.4%)
		Severe	1 (2.2%)	(0.1%, 11.5%)	0	(0.0%, 8.4%)	1 (3.2%)	(0.1%, 16.7%)	2 (2.7%)	(0.3%, 9.5%)
	Week 24	None	22 (51.2%)	(35.5%, 66.7%)	24 (60.0%)	(43.3%, 75.1%)	7 (25.9%)	(11.1%, 46.3%)	39 (57.4%)	(44.8%, 69.3%)
		Mild	14 (32.6%)	(19.1%, 48.5%)	11 (27.5%)	(14.6%, 43.9%)	14 (51.9%)	(31.9%, 71.3%)	21 (30.9%)	(20.2%, 43.3%)
		Moderate	7 (16.3%)	(6.8%, 30.7%)	5 (12.5%)	(4.2%, 26.8%)	6 (22.2%)	(8.6%, 42.3%)	7 (10.3%)	(4.2%, 20.1%)
		Severe	0	(0.0%, 8.2%)	0	(0.0%, 8.8%)	0	(0.0%, 12.8%)	1 (1.5%)	(0.0%, 7.9%)
Sneezing Symptom Score median	Week 8	None	29 (69.0%)	(52.9%, 82.4%)	29 (69.0%)	(52.9%, 82.4%)	23 (74.2%)	(55.4%, 88.1%)	52 (69.3%)	(57.6%, 79.5%)
		Mild	13 (31.0%)	(17.6%, 47.1%)	12 (28.6%)	(15.7%, 44.6%)	7 (22.6%)	(9.6%, 41.1%)	20 (26.7%)	(17.1%, 38.1%)
		Moderate	0	(0.0%, 8.4%)	1 (2.4%)	(0.1%, 12.6%)	1 (3.2%)	(0.1%, 16.7%)	3 (4.0%)	(0.8%, 11.2%)
	Week 12	None	34 (73.9%)	(58.9%, 85.7%)	28 (66.7%)	(50.5%, 80.4%)	21 (67.7%)	(48.6%, 83.3%)	53 (72.6%)	(60.9%, 82.4%)
		Mild	10 (21.7%)	(10.9%, 36.4%)	13 (31.0%)	(17.6%, 47.1%)	10 (32.3%)	(16.7%, 51.4%)	16 (21.9%)	(13.1%, 33.1%)
		Moderate	2 (4.3%)	(0.5%, 14.8%)	1 (2.4%)	(0.1%, 12.6%)	0	(0.0%, 11.2%)	4 (5.5%)	(1.5%, 13.4%)
	Week 24	None	28 (65.1%)	(49.1%, 79.0%)	27 (67.5%)	(50.9%, 81.4%)	17 (63.0%)	(42.4%, 80.6%)	48 (70.6%)	(58.3%, 81.0%)
		Mild	14 (32.6%)	(19.1%, 48.5%)	12 (30.0%)	(16.6%, 46.5%)	8 (29.6%)	(13.8%, 50.2%)	18 (26.5%)	(16.5%, 38.6%)
		Moderate	1 (2.3%)	(0.1%, 12.3%)	1 (2.5%)	(0.1%, 13.2%)	2 (7.4%)	(0.9%, 24.3%)	2 (2.9%)	(0.4%, 10.2%)

* Confidence intervals calculated using Clopper-Pearson method.

Table 14.37 Change from baseline of Weekly median individual symptom score at Weeks 8, 12 and 24, FAS (before and after first interim analysis)

			Old Active + Active N=49		Low amplitude control + Active N=47		New Active + Active N=32		Placebo + Active N=79	
Parameter	**Visit**	**Score**	**n (%)**	**95% CI***	**n (%)**	**95% CI***	**n (%)**	**95% CI***	**n (%)**	**95% CI***
Nasal Congestion Symptom Score median	8	Improved	23 (54.8%)	(38.7%, 70.2%)	22 (52.4%)	(36.4%, 68.0%)	17 (54.8%)	(36.0%, 72.7%)	34 (45.3%)	(33.8%, 57.3%)
		No change	18 (42.9%)	(27.7%, 59.0%)	17 (40.5%)	(25.6%, 56.7%)	13 (41.9%)	(24.5%, 60.9%)	38 (50.7%)	(38.9%, 62.4%)
		Worsened	1 (2.4%)	(0.1%, 12.6%)	3 (7.1%)	(1.5%, 19.5%)	1 (3.2%)	(0.1%, 16.7%)	3 (4.0%)	(0.8%, 11.2%)
	12	Improved	22 (47.8%)	(32.9%, 63.1%)	22 (52.4%)	(36.4%, 68.0%)	15 (48.4%)	(30.2%, 66.9%)	28 (38.4%)	(27.2%, 50.5%)
		No change	21 (45.7%)	(30.9%, 61.0%)	18 (42.9%)	(27.7%, 59.0%)	15 (48.4%)	(30.2%, 66.9%)	37 (50.7%)	(38.7%, 62.6%)
		Worsened	3 (6.5%)	(1.4%, 17.9%)	2 (4.8%)	(0.6%, 16.2%)	1 (3.2%)	(0.1%, 16.7%)	8 (11.0%)	(4.9%, 20.5%)
	24	Improved	18 (41.9%)	(27.0%, 57.9%)	16 (40.0%)	(24.9%, 56.7%)	16 (59.3%)	(38.8%, 77.6%)	36 (52.9%)	(40.4%, 65.2%)
		No change	20 (46.5%)	(31.2%, 62.3%)	22 (55.0%)	(38.5%, 70.7%)	8 (29.6%)	(13.8%, 50.2%)	25 (36.8%)	(25.4%, 49.3%)
		Worsened	5 (11.6%)	(3.9%, 25.1%)	2 (5.0%)	(0.6%, 16.9%)	3 (11.1%)	(2.4%, 29.2%)	7 (10.3%)	(4.2%, 20.1%)
Postnasal Drip Symptom Score median	8	Improved	12 (28.6%)	(15.7%, 44.6%)	12 (28.6%)	(15.7%, 44.6%)	8 (25.8%)	(11.9%, 44.6%)	13 (17.3%)	(9.6%, 27.8%)
		No change	27 (64.3%)	(48.0%, 78.4%)	28 (66.7%)	(50.5%, 80.4%)	22 (71.0%)	(52.0%, 85.8%)	48 (64.0%)	(52.1%, 74.8%)
		Worsened	3 (7.1%)	(1.5%, 19.5%)	2 (4.8%)	(0.6%, 16.2%)	1 (3.2%)	(0.1%, 16.7%)	14 (18.7%)	(10.6%, 29.3%)
	12	Improved	12 (26.1%)	(14.3%, 41.1%)	12 (28.6%)	(15.7%, 44.6%)	6 (19.4%)	(7.5%, 37.5%)	16 (21.9%)	(13.1%, 33.1%)
		No change	27 (58.7%)	(43.2%, 73.0%)	26 (61.9%)	(45.6%, 76.4%)	23 (74.2%)	(55.4%, 88.1%)	41 (56.2%)	(44.1%, 67.8%)
		Worsened	7 (15.2%)	(6.3%, 28.9%)	4 (9.5%)	(2.7%, 22.6%)	2 (6.5%)	(0.8%, 21.4%)	16 (21.9%)	(13.1%, 33.1%)
	24	Improved	13 (30.2%)	(17.2%, 46.1%)	13 (32.5%)	(18.6%, 49.1%)	3 (11.1%)	(2.4%, 29.2%)	20 (29.4%)	(19.0%, 41.7%)
		No change	22 (51.2%)	(35.5%, 66.7%)	23 (57.5%)	(40.9%, 73.0%)	20 (74.1%)	(53.7%, 88.9%)	41 (60.3%)	(47.7%, 72.0%)
		Worsened	8 (18.6%)	(8.4%, 33.4%)	4 (10.0%)	(2.8%, 23.7%)	4 (14.8%)	(4.2%, 33.7%)	7 (10.3%)	(4.2%, 20.1%)
Rhinorrhea Symptom Score median	8	Improved	16 (38.1%)	(23.6%, 54.4%)	17 (40.5%)	(25.6%, 56.7%)	10 (32.3%)	(16.7%, 51.4%)	23 (30.7%)	(20.5%, 42.4%)
		No change	21 (50.0%)	(34.2%, 65.8%)	23 (54.8%)	(38.7%, 70.2%)	18 (58.1%)	(39.1%, 75.5%)	42 (56.0%)	(44.1%, 67.5%)
		Worsened	5 (11.9%)	(4.0%, 25.6%)	2 (4.8%)	(0.6%, 16.2%)	3 (9.7%)	(2.0%, 25.8%)	10 (13.3%)	(6.6%, 23.2%)
	12	Improved	15 (32.6%)	(19.5%, 48.0%)	18 (42.9%)	(27.7%, 59.0%)	8 (25.8%)	(11.9%, 44.6%)	21 (28.8%)	(18.8%, 40.6%)
		No change	27 (58.7%)	(43.2%, 73.0%)	20 (47.6%)	(32.0%, 63.6%)	20 (64.5%)	(45.4%, 80.8%)	43 (58.9%)	(46.8%, 70.3%)
		Worsened	4 (8.7%)	(2.4%, 20.8%)	4 (9.5%)	(2.7%, 22.6%)	3 (9.7%)	(2.0%, 25.8%)	9 (12.3%)	(5.8%, 22.1%)

			Old Active + Active N=49		Low amplitude control + Active N=47		New Active + Active N=32		Placebo + Active N=79	
Parameter	**Visit**	**Score**	**n (%)**	**95% CI***	**n (%)**	**95% CI***	**n (%)**	**95% CI***	**n (%)**	**95% CI***
	24	Improved	13 (30.2%)	(17.2%, 46.1%)	17 (42.5%)	(27.0%, 59.1%)	9 (33.3%)	(16.5%, 54.0%)	22 (32.4%)	(21.5%, 44.8%)
		No change	20 (46.5%)	(31.2%, 62.3%)	18 (45.0%)	(29.3%, 61.5%)	16 (59.3%)	(38.8%, 77.6%)	44 (64.7%)	(52.2%, 75.9%)
		Worsened	10 (23.3%)	(11.8%, 38.6%)	5 (12.5%)	(4.2%, 26.8%)	2 (7.4%)	(0.9%, 24.3%)	2 (2.9%)	(0.4%, 10.2%)
Sneezing Symptom Score median	8	Improved	8 (19.0%)	(8.6%, 34.1%)	5 (11.9%)	(4.0%, 25.6%)	10 (32.3%)	(16.7%, 51.4%)	10 (13.3%)	(6.6%, 23.2%)
		No change	31 (73.8%)	(58.0%, 86.1%)	34 (81.0%)	(65.9%, 91.4%)	20 (64.5%)	(45.4%, 80.8%)	52 (69.3%)	(57.6%, 79.5%)
		Worsened	3 (7.1%)	(1.5%, 19.5%)	3 (7.1%)	(1.5%, 19.5%)	1 (3.2%)	(0.1%, 16.7%)	13 (17.3%)	(9.6%, 27.8%)
	12	Improved	7 (15.2%)	(6.3%, 28.9%)	8 (19.0%)	(8.6%, 34.1%)	9 (29.0%)	(14.2%, 48.0%)	12 (16.4%)	(8.8%, 27.0%)
		No change	36 (78.3%)	(63.6%, 89.1%)	28 (66.7%)	(50.5%, 80.4%)	20 (64.5%)	(45.4%, 80.8%)	47 (64.4%)	(52.3%, 75.3%)
		Worsened	3 (6.5%)	(1.4%, 17.9%)	6 (14.3%)	(5.4%, 28.5%)	2 (6.5%)	(0.8%, 21.4%)	14 (19.2%)	(10.9%, 30.1%)
	24	Improved	6 (14.0%)	(5.3%, 27.9%)	6 (15.0%)	(5.7%, 29.8%)	5 (18.5%)	(6.3%, 38.1%)	8 (11.8%)	(5.2%, 21.9%)
		No change	33 (76.7%)	(61.4%, 88.2%)	29 (72.5%)	(56.1%, 85.4%)	21 (77.8%)	(57.7%, 91.4%)	47 (69.1%)	(56.7%, 79.8%)
		Worsened	4 (9.3%)	(2.6%, 22.1%)	5 (12.5%)	(4.2%, 26.8%)	1 (3.7%)	(0.1%, 19.0%)	13 (19.1%)	(10.6%, 30.5%)

* Confidence intervals calculated using Clopper-Pearson method.

Table 14.38 SNOT-22 individual items up to Week 4, FAS

			Active N=81		Placebo N=79	
Parameter	**Week**	**Score**	**n (%)**	**95% CI***	**n (%)**	**95% CI***
Need to blow nose	Week -1 Screening	No problem	8 (9.9%)	(4.4%, 18.5%)	7 (8.9%)	(3.6%, 17.4%)
		Very mild problem	9 (11.1%)	(5.2%, 20.0%)	10 (12.7%)	(6.2%, 22.0%)
		Mild or slight problem	7 (8.6%)	(3.5%, 17.0%)	17 (21.5%)	(13.1%, 32.2%)
		Moderate problem	25 (30.9%)	(21.1%, 42.1%)	26 (32.9%)	(22.7%, 44.4%)
		Severe problem	25 (30.9%)	(21.1%, 42.1%)	12 (15.2%)	(8.1%, 25.0%)
		Problem as bad as it can be	7 (8.6%)	(3.5%, 17.0%)	7 (8.9%)	(3.6%, 17.4%)
	Week 4	No problem	8 (10.0%)	(4.4%, 18.8%)	5 (6.5%)	(2.1%, 14.5%)
		Very mild problem	15 (18.8%)	(10.9%, 29.0%)	16 (20.8%)	(12.4%, 31.5%)
		Mild or slight problem	23 (28.8%)	(19.2%, 40.0%)	17 (22.1%)	(13.4%, 33.0%)
		Moderate problem	19 (23.8%)	(14.9%, 34.6%)	17 (22.1%)	(13.4%, 33.0%)
		Severe problem	11 (13.8%)	(7.1%, 23.3%)	17 (22.1%)	(13.4%, 33.0%)
		Problem as bad as it can be	4 (5.0%)	(1.4%, 12.3%)	5 (6.5%)	(2.1%, 14.5%)
Sneezing	Screening	No problem	19 (23.5%)	(14.8%, 34.2%)	15 (19.0%)	(11.0%, 29.4%)
		Very mild problem	22 (27.2%)	(17.9%, 38.2%)	20 (25.3%)	(16.2%, 36.4%)
		Mild or slight problem	14 (17.3%)	(9.8%, 27.3%)	23 (29.1%)	(19.4%, 40.4%)
		Moderate problem	16 (19.8%)	(11.7%, 30.1%)	13 (16.5%)	(9.1%, 26.5%)
		Severe problem	9 (11.1%)	(5.2%, 20.0%)	7 (8.9%)	(3.6%, 17.4%)
		Problem as bad as it can be	1 (1.2%)	(0.0%, 6.7%)	1 (1.3%)	(0.0%, 6.9%)
	Week 4	No problem	26 (32.5%)	(22.4%, 43.9%)	16 (20.8%)	(12.4%, 31.5%)
		Very mild problem	20 (25.0%)	(16.0%, 35.9%)	28 (36.4%)	(25.7%, 48.1%)
		Mild or slight problem	19 (23.8%)	(14.9%, 34.6%)	19 (24.7%)	(15.6%, 35.8%)
		Moderate problem	11 (13.8%)	(7.1%, 23.3%)	8 (10.4%)	(4.6%, 19.4%)
		Severe problem	4 (5.0%)	(1.4%, 12.3%)	5 (6.5%)	(2.1%, 14.5%)
		Problem as bad as it can be	0	(0.0%, 4.5%)	1 (1.3%)	(0.0%, 7.0%)
Runny nose	Screening	No problem	18 (22.2%)	(13.7%, 32.8%)	10 (12.7%)	(6.2%, 22.0%)
		Very mild problem	18 (22.2%)	(13.7%, 32.8%)	26 (32.9%)	(22.7%, 44.4%)
		Mild or slight problem	13 (16.0%)	(8.8%, 25.9%)	13 (16.5%)	(9.1%, 26.5%)
		Moderate problem	13 (16.0%)	(8.8%, 25.9%)	14 (17.7%)	(10.0%, 27.9%)
		Severe problem	14 (17.3%)	(9.8%, 27.3%)	11 (13.9%)	(7.2%, 23.5%)
		Problem as bad as it can be	5 (6.2%)	(2.0%, 13.8%)	5 (6.3%)	(2.1%, 14.2%)
	Week 4	No problem	20 (25.0%)	(16.0%, 35.9%)	12 (15.6%)	(8.3%, 25.6%)
		Very mild problem	19 (23.8%)	(14.9%, 34.6%)	19 (24.7%)	(15.6%, 35.8%)
		Mild or slight problem	14 (17.5%)	(9.9%, 27.6%)	18 (23.4%)	(14.5%, 34.4%)
		Moderate problem	17 (21.3%)	(12.9%, 31.8%)	10 (13.0%)	(6.4%, 22.6%)
		Severe problem	8 (10.0%)	(4.4%, 18.8%)	15 (19.5%)	(11.3%, 30.1%)
		Problem as bad as it can be	2 (2.5%)	(0.3%, 8.7%)	3 (3.9%)	(0.8%, 11.0%)
Blockage/congestion of nose	Screening	No problem	0	(0.0%, 4.5%)	0	(0.0%, 4.6%)
		Very mild problem	0	(0.0%, 4.5%)	0	(0.0%, 4.6%)
		Mild or slight problem	1 (1.2%)	(0.0%, 6.7%)	2 (2.5%)	(0.3%, 8.8%)
		Moderate problem	18 (22.2%)	(13.7%, 32.8%)	15 (19.0%)	(11.0%, 29.4%)
		Severe problem	37 (45.7%)	(34.6%, 57.1%)	37 (46.8%)	(35.5%, 58.4%)
		Problem as bad as it can be	25 (30.9%)	(21.1%, 42.1%)	25 (31.6%)	(21.6%, 43.1%)

Parameter	Week	Score	Active N=81 n (%)	Active N=81 95% CI*	Placebo N=79 n (%)	Placebo N=79 95% CI*
	Week 4	No problem	2 (2.5%)	(0.3%, 8.7%)	1 (1.3%)	(0.0%, 7.0%)
		Very mild problem	6 (7.5%)	(2.8%, 15.6%)	2 (2.6%)	(0.3%, 9.1%)
		Mild or slight problem	11 (13.8%)	(7.1%, 23.3%)	4 (5.2%)	(1.4%, 12.8%)
		Moderate problem	16 (20.0%)	(11.9%, 30.4%)	17 (22.1%)	(13.4%, 33.0%)
		Severe problem	39 (48.8%)	(37.4%, 60.2%)	38 (49.4%)	(37.8%, 61.0%)
		Problem as bad as it can be	6 (7.5%)	(2.8%, 15.6%)	15 (19.5%)	(11.3%, 30.1%)
Sense of smell/taste	Screening	No problem	25 (30.9%)	(21.1%, 42.1%)	34 (43.0%)	(31.9%, 54.7%)
		Very mild problem	18 (22.2%)	(13.7%, 32.8%)	17 (21.5%)	(13.1%, 32.2%)
		Mild or slight problem	13 (16.0%)	(8.8%, 25.9%)	10 (12.7%)	(6.2%, 22.0%)
		Moderate problem	13 (16.0%)	(8.8%, 25.9%)	11 (13.9%)	(7.2%, 23.5%)
		Severe problem	6 (7.4%)	(2.8%, 15.4%)	5 (6.3%)	(2.1%, 14.2%)
		Problem as bad as it can be	6 (7.4%)	(2.8%, 15.4%)	2 (2.5%)	(0.3%, 8.8%)
	Week 4	No problem	36 (45.0%)	(33.8%, 56.5%)	32 (41.6%)	(30.4%, 53.4%)
		Very mild problem	15 (18.8%)	(10.9%, 29.0%)	15 (19.5%)	(11.3%, 30.1%)
		Mild or slight problem	12 (15.0%)	(8.0%, 24.7%)	13 (16.9%)	(9.3%, 27.1%)
		Moderate problem	8 (10.0%)	(4.4%, 18.8%)	10 (13.0%)	(6.4%, 22.6%)
		Severe problem	6 (7.5%)	(2.8%, 15.6%)	6 (7.8%)	(2.9%, 16.2%)
		Problem as bad as it can be	3 (3.8%)	(0.8%, 10.6%)	1 (1.3%)	(0.0%, 7.0%)
Cough	Screening	No problem	45 (55.6%)	(44.1%, 66.6%)	38 (48.1%)	(36.7%, 59.6%)
		Very mild problem	15 (18.5%)	(10.8%, 28.7%)	17 (21.5%)	(13.1%, 32.2%)
		Mild or slight problem	13 (16.0%)	(8.8%, 25.9%)	11 (13.9%)	(7.2%, 23.5%)
		Moderate problem	4 (4.9%)	(1.4%, 12.2%)	11 (13.9%)	(7.2%, 23.5%)
		Severe problem	4 (4.9%)	(1.4%, 12.2%)	1 (1.3%)	(0.0%, 6.9%)
		Problem as bad as it can be	0	(0.0%, 4.5%)	1 (1.3%)	(0.0%, 6.9%)
	Week 4	No problem	57 (71.3%)	(60.0%, 80.8%)	38 (49.4%)	(37.8%, 61.0%)
		Very mild problem	5 (6.3%)	(2.1%, 14.0%)	12 (15.6%)	(8.3%, 25.6%)
		Mild or slight problem	9 (11.3%)	(5.3%, 20.3%)	17 (22.1%)	(13.4%, 33.0%)
		Moderate problem	4 (5.0%)	(1.4%, 12.3%)	5 (6.5%)	(2.1%, 14.5%)
		Severe problem	4 (5.0%)	(1.4%, 12.3%)	4 (5.2%)	(1.4%, 12.8%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 6.8%)	1 (1.3%)	(0.0%, 7.0%)
Post-nasal discharge	Screening	No problem	26 (32.1%)	(22.2%, 43.4%)	20 (25.3%)	(16.2%, 36.4%)
		Very mild problem	11 (13.6%)	(7.0%, 23.0%)	16 (20.3%)	(12.0%, 30.8%)
		Mild or slight problem	13 (16.0%)	(8.8%, 25.9%)	11 (13.9%)	(7.2%, 23.5%)
		Moderate problem	12 (14.8%)	(7.9%, 24.4%)	15 (19.0%)	(11.0%, 29.4%)
		Severe problem	17 (21.0%)	(12.7%, 31.5%)	12 (15.2%)	(8.1%, 25.0%)
		Problem as bad as it can be	2 (2.5%)	(0.3%, 8.6%)	5 (6.3%)	(2.1%, 14.2%)

Parameter	Week	Score	Active N=81 n (%)	Active N=81 95% CI*	Placebo N=79 n (%)	Placebo N=79 95% CI*
	Week 4	No problem	25 (31.3%)	(21.3%, 42.6%)	18 (23.4%)	(14.5%, 34.4%)
		Very mild problem	15 (18.8%)	(10.9%, 29.0%)	13 (16.9%)	(9.3%, 27.1%)
		Mild or slight problem	16 (20.0%)	(11.9%, 30.4%)	13 (16.9%)	(9.3%, 27.1%)
		Moderate problem	10 (12.5%)	(6.2%, 21.8%)	17 (22.1%)	(13.4%, 33.0%)
		Severe problem	11 (13.8%)	(7.1%, 23.3%)	14 (18.2%)	(10.3%, 28.6%)
		Problem as bad as it can be	3 (3.8%)	(0.8%, 10.6%)	2 (2.6%)	(0.3%, 9.1%)
Thick nasal discharge	Screening	No problem	32 (39.5%)	(28.8%, 51.0%)	36 (45.6%)	(34.3%, 57.2%)
		Very mild problem	10 (12.3%)	(6.1%, 21.5%)	13 (16.5%)	(9.1%, 26.5%)
		Mild or slight problem	19 (23.5%)	(14.8%, 34.2%)	17 (21.5%)	(13.1%, 32.2%)
		Moderate problem	12 (14.8%)	(7.9%, 24.4%)	6 (7.6%)	(2.8%, 15.8%)
		Severe problem	6 (7.4%)	(2.8%, 15.4%)	5 (6.3%)	(2.1%, 14.2%)
		Problem as bad as it can be	2 (2.5%)	(0.3%, 8.6%)	2 (2.5%)	(0.3%, 8.8%)
	Week 4	No problem	42 (52.5%)	(41.0%, 63.8%)	39 (50.6%)	(39.0%, 62.2%)
		Very mild problem	10 (12.5%)	(6.2%, 21.8%)	14 (18.2%)	(10.3%, 28.6%)
		Mild or slight problem	16 (20.0%)	(11.9%, 30.4%)	7 (9.1%)	(3.7%, 17.8%)
		Moderate problem	8 (10.0%)	(4.4%, 18.8%)	16 (20.8%)	(12.4%, 31.5%)
		Severe problem	4 (5.0%)	(1.4%, 12.3%)	1 (1.3%)	(0.0%, 7.0%)
		Problem as bad as it can be	0	(0.0%, 4.5%)	0	(0.0%, 4.7%)
Ear fullnes	Screening	No problem	30 (37.0%)	(26.6%, 48.5%)	34 (43.0%)	(31.9%, 54.7%)
		Very mild problem	13 (16.0%)	(8.8%, 25.9%)	14 (17.7%)	(10.0%, 27.9%)
		Mild or slight problem	13 (16.0%)	(8.8%, 25.9%)	12 (15.2%)	(8.1%, 25.0%)
		Moderate problem	14 (17.3%)	(9.8%, 27.3%)	11 (13.9%)	(7.2%, 23.5%)
		Severe problem	7 (8.6%)	(3.5%, 17.0%)	5 (6.3%)	(2.1%, 14.2%)
		Problem as bad as it can be	4 (4.9%)	(1.4%, 12.2%)	3 (3.8%)	(0.8%, 10.7%)
	Week 4	No problem	38 (47.5%)	(36.2%, 59.0%)	37 (48.1%)	(36.5%, 59.7%)
		Very mild problem	17 (21.3%)	(12.9%, 31.8%)	20 (26.0%)	(16.6%, 37.2%)
		Mild or slight problem	12 (15.0%)	(8.0%, 24.7%)	9 (11.7%)	(5.5%, 21.0%)
		Moderate problem	4 (5.0%)	(1.4%, 12.3%)	5 (6.5%)	(2.1%, 14.5%)
		Severe problem	9 (11.3%)	(5.3%, 20.3%)	4 (5.2%)	(1.4%, 12.8%)
		Problem as bad as it can be	0	(0.0%, 4.5%)	2 (2.6%)	(0.3%, 9.1%)
Dizziness	Screening	No problem	49 (60.5%)	(49.0%, 71.2%)	53 (67.1%)	(55.6%, 77.3%)
		Very mild problem	13 (16.0%)	(8.8%, 25.9%)	10 (12.7%)	(6.2%, 22.0%)
		Mild or slight problem	9 (11.1%)	(5.2%, 20.0%)	9 (11.4%)	(5.3%, 20.5%)
		Moderate problem	6 (7.4%)	(2.8%, 15.4%)	4 (5.1%)	(1.4%, 12.5%)
		Severe problem	3 (3.7%)	(0.8%, 10.4%)	3 (3.8%)	(0.8%, 10.7%)
		Problem as bad as it can be	1 (1.2%)	(0.0%, 6.7%)	0	(0.0%, 4.6%)

Parameter	Week	Score	Active N=81		Placebo N=79	
			n (%)	95% CI*	n (%)	95% CI*
	Week 4	No problem	54 (67.5%)	(56.1%, 77.6%)	52 (67.5%)	(55.9%, 77.8%)
		Very mild problem	14 (17.5%)	(9.9%, 27.6%)	13 (16.9%)	(9.3%, 27.1%)
		Mild or slight problem	4 (5.0%)	(1.4%, 12.3%)	8 (10.4%)	(4.6%, 19.4%)
		Moderate problem	6 (7.5%)	(2.8%, 15.6%)	3 (3.9%)	(0.8%, 11.0%)
		Severe problem	2 (2.5%)	(0.3%, 8.7%)	1 (1.3%)	(0.0%, 7.0%)
		Problem as bad as it can be	0	(0.0%, 4.5%)	0	(0.0%, 4.7%)
Ear pain	Screening	No problem	60 (74.1%)	(63.1%, 83.2%)	58 (73.4%)	(62.3%, 82.7%)
		Very mild problem	8 (9.9%)	(4.4%, 18.5%)	11 (13.9%)	(7.2%, 23.5%)
		Mild or slight problem	8 (9.9%)	(4.4%, 18.5%)	7 (8.9%)	(3.6%, 17.4%)
		Moderate problem	5 (6.2%)	(2.0%, 13.8%)	2 (2.5%)	(0.3%, 8.8%)
		Severe problem	0	(0.0%, 4.5%)	1 (1.3%)	(0.0%, 6.9%)
		Problem as bad as it can be	0	(0.0%, 4.5%)	0	(0.0%, 4.6%)
	Week 4	No problem	63 (78.8%)	(68.2%, 87.1%)	59 (76.6%)	(65.6%, 85.5%)
		Very mild problem	12 (15.0%)	(8.0%, 24.7%)	8 (10.4%)	(4.6%, 19.4%)
		Mild or slight problem	2 (2.5%)	(0.3%, 8.7%)	4 (5.2%)	(1.4%, 12.8%)
		Moderate problem	2 (2.5%)	(0.3%, 8.7%)	4 (5.2%)	(1.4%, 12.8%)
		Severe problem	0	(0.0%, 4.5%)	2 (2.6%)	(0.3%, 9.1%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 6.8%)	0	(0.0%, 4.7%)
Facial pain/pressure	Screening	No problem	48 (59.3%)	(47.8%, 70.1%)	54 (68.4%)	(56.9%, 78.4%)
		Very mild problem	9 (11.1%)	(5.2%, 20.0%)	7 (8.9%)	(3.6%, 17.4%)
		Mild or slight problem	11 (13.6%)	(7.0%, 23.0%)	4 (5.1%)	(1.4%, 12.5%)
		Moderate problem	4 (4.9%)	(1.4%, 12.2%)	5 (6.3%)	(2.1%, 14.2%)
		Severe problem	6 (7.4%)	(2.8%, 15.4%)	7 (8.9%)	(3.6%, 17.4%)
		Problem as bad as it can be	3 (3.7%)	(0.8%, 10.4%)	2 (2.5%)	(0.3%, 8.8%)
	Week 4	No problem	57 (71.3%)	(60.0%, 80.8%)	50 (64.9%)	(53.2%, 75.5%)
		Very mild problem	4 (5.0%)	(1.4%, 12.3%)	13 (16.9%)	(9.3%, 27.1%)
		Mild or slight problem	11 (13.8%)	(7.1%, 23.3%)	4 (5.2%)	(1.4%, 12.8%)
		Moderate problem	4 (5.0%)	(1.4%, 12.3%)	6 (7.8%)	(2.9%, 16.2%)
		Severe problem	2 (2.5%)	(0.3%, 8.7%)	4 (5.2%)	(1.4%, 12.8%)
		Problem as bad as it can be	2 (2.5%)	(0.3%, 8.7%)	0	(0.0%, 4.7%)
Difficulty falling asleep	Screening	No problem	27 (33.3%)	(23.2%, 44.7%)	33 (41.8%)	(30.8%, 53.4%)
		Very mild problem	14 (17.3%)	(9.8%, 27.3%)	9 (11.4%)	(5.3%, 20.5%)
		Mild or slight problem	8 (9.9%)	(4.4%, 18.5%)	9 (11.4%)	(5.3%, 20.5%)
		Moderate problem	13 (16.0%)	(8.8%, 25.9%)	8 (10.1%)	(4.5%, 19.0%)
		Severe problem	12 (14.8%)	(7.9%, 24.4%)	14 (17.7%)	(10.0%, 27.9%)
		Problem as bad as it can be	7 (8.6%)	(3.5%, 17.0%)	6 (7.6%)	(2.8%, 15.8%)

Parameter	Week	Score	Active N=81		Placebo N=79	
			n (%)	95% CI*	n (%)	95% CI*
	Week 4	No problem	28 (35.0%)	(24.7%, 46.5%)	26 (33.8%)	(23.4%, 45.4%)
		Very mild problem	17 (21.3%)	(12.9%, 31.8%)	13 (16.9%)	(9.3%, 27.1%)
		Mild or slight problem	14 (17.5%)	(9.9%, 27.6%)	14 (18.2%)	(10.3%, 28.6%)
		Moderate problem	11 (13.8%)	(7.1%, 23.3%)	9 (11.7%)	(5.5%, 21.0%)
		Severe problem	9 (11.3%)	(5.3%, 20.3%)	12 (15.6%)	(8.3%, 25.6%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 6.8%)	3 (3.9%)	(0.8%, 11.0%)
Waking up at night	Screening	No problem	15 (18.5%)	(10.8%, 28.7%)	12 (15.2%)	(8.1%, 25.0%)
		Very mild problem	11 (13.6%)	(7.0%, 23.0%)	14 (17.7%)	(10.0%, 27.9%)
		Mild or slight problem	15 (18.5%)	(10.8%, 28.7%)	12 (15.2%)	(8.1%, 25.0%)
		Moderate problem	14 (17.3%)	(9.8%, 27.3%)	15 (19.0%)	(11.0%, 29.4%)
		Severe problem	15 (18.5%)	(10.8%, 28.7%)	20 (25.3%)	(16.2%, 36.4%)
		Problem as bad as it can be	11 (13.6%)	(7.0%, 23.0%)	6 (7.6%)	(2.8%, 15.8%)
	Week 4	No problem	16 (20.0%)	(11.9%, 30.4%)	11 (14.3%)	(7.4%, 24.1%)
		Very mild problem	11 (13.8%)	(7.1%, 23.3%)	15 (19.5%)	(11.3%, 30.1%)
		Mild or slight problem	20 (25.0%)	(16.0%, 35.9%)	8 (10.4%)	(4.6%, 19.4%)
		Moderate problem	18 (22.5%)	(13.9%, 33.2%)	25 (32.5%)	(22.2%, 44.1%)
		Severe problem	10 (12.5%)	(6.2%, 21.8%)	14 (18.2%)	(10.3%, 28.6%)
		Problem as bad as it can be	5 (6.3%)	(2.1%, 14.0%)	4 (5.2%)	(1.4%, 12.8%)
Lack of good night's sleep	Screening	No problem	14 (17.3%)	(9.8%, 27.3%)	15 (19.0%)	(11.0%, 29.4%)
		Very mild problem	12 (14.8%)	(7.9%, 24.4%)	14 (17.7%)	(10.0%, 27.9%)
		Mild or slight problem	17 (21.0%)	(12.7%, 31.5%)	10 (12.7%)	(6.2%, 22.0%)
		Moderate problem	15 (18.5%)	(10.8%, 28.7%)	14 (17.7%)	(10.0%, 27.9%)
		Severe problem	15 (18.5%)	(10.8%, 28.7%)	18 (22.8%)	(14.1%, 33.6%)
		Problem as bad as it can be	8 (9.9%)	(4.4%, 18.5%)	8 (10.1%)	(4.5%, 19.0%)
	Week 4	No problem	19 (23.8%)	(14.9%, 34.6%)	15 (19.5%)	(11.3%, 30.1%)
		Very mild problem	14 (17.5%)	(9.9%, 27.6%)	15 (19.5%)	(11.3%, 30.1%)
		Mild or slight problem	16 (20.0%)	(11.9%, 30.4%)	11 (14.3%)	(7.4%, 24.1%)
		Moderate problem	16 (20.0%)	(11.9%, 30.4%)	20 (26.0%)	(16.6%, 37.2%)
		Severe problem	12 (15.0%)	(8.0%, 24.7%)	14 (18.2%)	(10.3%, 28.6%)
		Problem as bad as it can be	3 (3.8%)	(0.8%, 10.6%)	2 (2.6%)	(0.3%, 9.1%)
Waking up tired	Screening	No problem	10 (12.3%)	(6.1%, 21.5%)	12 (15.2%)	(8.1%, 25.0%)
		Very mild problem	10 (12.3%)	(6.1%, 21.5%)	8 (10.1%)	(4.5%, 19.0%)
		Mild or slight problem	13 (16.0%)	(8.8%, 25.9%)	11 (13.9%)	(7.2%, 23.5%)
		Moderate problem	20 (24.7%)	(15.8%, 35.5%)	15 (19.0%)	(11.0%, 29.4%)
		Severe problem	18 (22.2%)	(13.7%, 32.8%)	24 (30.4%)	(20.5%, 41.8%)
		Problem as bad as it can be	10 (12.3%)	(6.1%, 21.5%)	9 (11.4%)	(5.3%, 20.5%)

Parameter	Week	Score	Active N=81		Placebo N=79	
			n (%)	95% CI*	n (%)	95% CI*
	Week 4	No problem	13 (16.3%)	(8.9%, 26.2%)	8 (10.4%)	(4.6%, 19.4%)
		Very mild problem	19 (23.8%)	(14.9%, 34.6%)	7 (9.1%)	(3.7%, 17.8%)
		Mild or slight problem	14 (17.5%)	(9.9%, 27.6%)	15 (19.5%)	(11.3%, 30.1%)
		Moderate problem	15 (18.8%)	(10.9%, 29.0%)	25 (32.5%)	(22.2%, 44.1%)
		Severe problem	13 (16.3%)	(8.9%, 26.2%)	13 (16.9%)	(9.3%, 27.1%)
		Problem as bad as it can be	6 (7.5%)	(2.8%, 15.6%)	9 (11.7%)	(5.5%, 21.0%)
Fatigue	Screening	No problem	12 (14.8%)	(7.9%, 24.4%)	18 (22.8%)	(14.1%, 33.6%)
		Very mild problem	22 (27.2%)	(17.9%, 38.2%)	10 (12.7%)	(6.2%, 22.0%)
		Mild or slight problem	10 (12.3%)	(6.1%, 21.5%)	18 (22.8%)	(14.1%, 33.6%)
		Moderate problem	21 (25.9%)	(16.8%, 36.9%)	12 (15.2%)	(8.1%, 25.0%)
		Severe problem	10 (12.3%)	(6.1%, 21.5%)	21 (26.6%)	(17.3%, 37.7%)
		Problem as bad as it can be	6 (7.4%)	(2.8%, 15.4%)	0	(0.0%, 4.6%)
	Week 4	No problem	19 (23.8%)	(14.9%, 34.6%)	13 (16.9%)	(9.3%, 27.1%)
		Very mild problem	21 (26.3%)	(17.0%, 37.3%)	19 (24.7%)	(15.6%, 35.8%)
		Mild or slight problem	18 (22.5%)	(13.9%, 33.2%)	15 (19.5%)	(11.3%, 30.1%)
		Moderate problem	12 (15.0%)	(8.0%, 24.7%)	18 (23.4%)	(14.5%, 34.4%)
		Severe problem	7 (8.8%)	(3.6%, 17.2%)	9 (11.7%)	(5.5%, 21.0%)
		Problem as bad as it can be	3 (3.8%)	(0.8%, 10.6%)	3 (3.9%)	(0.8%, 11.0%)
Reduced productivity	Screening	No problem	25 (30.9%)	(21.1%, 42.1%)	27 (34.2%)	(23.9%, 45.7%)
		Very mild problem	20 (24.7%)	(15.8%, 35.5%)	14 (17.7%)	(10.0%, 27.9%)
		Mild or slight problem	15 (18.5%)	(10.8%, 28.7%)	21 (26.6%)	(17.3%, 37.7%)
		Moderate problem	14 (17.3%)	(9.8%, 27.3%)	12 (15.2%)	(8.1%, 25.0%)
		Severe problem	5 (6.2%)	(2.0%, 13.8%)	5 (6.3%)	(2.1%, 14.2%)
		Problem as bad as it can be	2 (2.5%)	(0.3%, 8.6%)	0	(0.0%, 4.6%)
	Week 4	No problem	34 (42.5%)	(31.5%, 54.1%)	23 (29.9%)	(20.0%, 41.4%)
		Very mild problem	14 (17.5%)	(9.9%, 27.6%)	29 (37.7%)	(26.9%, 49.4%)
		Mild or slight problem	17 (21.3%)	(12.9%, 31.8%)	13 (16.9%)	(9.3%, 27.1%)
		Moderate problem	11 (13.8%)	(7.1%, 23.3%)	10 (13.0%)	(6.4%, 22.6%)
		Severe problem	3 (3.8%)	(0.8%, 10.6%)	2 (2.6%)	(0.3%, 9.1%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 6.8%)	0	(0.0%, 4.7%)
Reduced concentration	Screening	No problem	25 (30.9%)	(21.1%, 42.1%)	26 (32.9%)	(22.7%, 44.4%)
		Very mild problem	21 (25.9%)	(16.8%, 36.9%)	21 (26.6%)	(17.3%, 37.7%)
		Mild or slight problem	17 (21.0%)	(12.7%, 31.5%)	15 (19.0%)	(11.0%, 29.4%)
		Moderate problem	8 (9.9%)	(4.4%, 18.5%)	12 (15.2%)	(8.1%, 25.0%)
		Severe problem	7 (8.6%)	(3.5%, 17.0%)	4 (5.1%)	(1.4%, 12.5%)
		Problem as bad as it can be	3 (3.7%)	(0.8%, 10.4%)	1 (1.3%)	(0.0%, 6.9%)

Parameter	Week	Score	Active N=81		Placebo N=79	
			n (%)	95% CI*	n (%)	95% CI*
	Week 4	No problem	36 (45.0%)	(33.8%, 56.5%)	27 (35.1%)	(24.5%, 46.8%)
		Very mild problem	16 (20.0%)	(11.9%, 30.4%)	26 (33.8%)	(23.4%, 45.4%)
		Mild or slight problem	16 (20.0%)	(11.9%, 30.4%)	14 (18.2%)	(10.3%, 28.6%)
		Moderate problem	6 (7.5%)	(2.8%, 15.6%)	6 (7.8%)	(2.9%, 16.2%)
		Severe problem	5 (6.3%)	(2.1%, 14.0%)	4 (5.2%)	(1.4%, 12.8%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 6.8%)	0	(0.0%, 4.7%)
Frustrated/restless/ irritable	Screening	No problem	20 (24.7%)	(15.8%, 35.5%)	34 (43.0%)	(31.9%, 54.7%)
		Very mild problem	19 (23.5%)	(14.8%, 34.2%)	15 (19.0%)	(11.0%, 29.4%)
		Mild or slight problem	16 (19.8%)	(11.7%, 30.1%)	6 (7.6%)	(2.8%, 15.8%)
		Moderate problem	14 (17.3%)	(9.8%, 27.3%)	15 (19.0%)	(11.0%, 29.4%)
		Severe problem	6 (7.4%)	(2.8%, 15.4%)	6 (7.6%)	(2.8%, 15.8%)
		Problem as bad as it can be	6 (7.4%)	(2.8%, 15.4%)	3 (3.8%)	(0.8%, 10.7%)
	Week 4	No problem	30 (37.5%)	(26.9%, 49.0%)	32 (41.6%)	(30.4%, 53.4%)
		Very mild problem	21 (26.3%)	(17.0%, 37.3%)	11 (14.3%)	(7.4%, 24.1%)
		Mild or slight problem	13 (16.3%)	(8.9%, 26.2%)	15 (19.5%)	(11.3%, 30.1%)
		Moderate problem	10 (12.5%)	(6.2%, 21.8%)	15 (19.5%)	(11.3%, 30.1%)
		Severe problem	3 (3.8%)	(0.8%, 10.6%)	3 (3.9%)	(0.8%, 11.0%)
		Problem as bad as it can be	3 (3.8%)	(0.8%, 10.6%)	1 (1.3%)	(0.0%, 7.0%)
Sad	Screening	No problem	42 (51.9%)	(40.5%, 63.1%)	47 (59.5%)	(47.9%, 70.4%)
		Very mild problem	16 (19.8%)	(11.7%, 30.1%)	13 (16.5%)	(9.1%, 26.5%)
		Mild or slight problem	8 (9.9%)	(4.4%, 18.5%)	12 (15.2%)	(8.1%, 25.0%)
		Moderate problem	9 (11.1%)	(5.2%, 20.0%)	6 (7.6%)	(2.8%, 15.8%)
		Severe problem	5 (6.2%)	(2.0%, 13.8%)	1 (1.3%)	(0.0%, 6.9%)
		Problem as bad as it can be	1 (1.2%)	(0.0%, 6.7%)	0	(0.0%, 4.6%)
	Week 4	No problem	39 (48.8%)	(37.4%, 60.2%)	47 (61.0%)	(49.2%, 72.0%)
		Very mild problem	19 (23.8%)	(14.9%, 34.6%)	17 (22.1%)	(13.4%, 33.0%)
		Mild or slight problem	15 (18.8%)	(10.9%, 29.0%)	10 (13.0%)	(6.4%, 22.6%)
		Moderate problem	2 (2.5%)	(0.3%, 8.7%)	3 (3.9%)	(0.8%, 11.0%)
		Severe problem	4 (5.0%)	(1.4%, 12.3%)	0	(0.0%, 4.7%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 6.8%)	0	(0.0%, 4.7%)
Embarrassed	Screening	No problem	19 (23.5%)	(14.8%, 34.2%)	18 (22.8%)	(14.1%, 33.6%)
		Very mild problem	10 (12.3%)	(6.1%, 21.5%)	13 (16.5%)	(9.1%, 26.5%)
		Mild or slight problem	12 (14.8%)	(7.9%, 24.4%)	12 (15.2%)	(8.1%, 25.0%)
		Moderate problem	14 (17.3%)	(9.8%, 27.3%)	19 (24.1%)	(15.1%, 35.0%)
		Severe problem	16 (19.8%)	(11.7%, 30.1%)	11 (13.9%)	(7.2%, 23.5%)
		Problem as bad as it can be	10 (12.3%)	(6.1%, 21.5%)	6 (7.6%)	(2.8%, 15.8%)
	Week 4	No problem	32 (40.0%)	(29.2%, 51.6%)	29 (37.7%)	(26.9%, 49.4%)
		Very mild problem	10 (12.5%)	(6.2%, 21.8%)	14 (18.2%)	(10.3%, 28.6%)
		Mild or slight problem	13 (16.3%)	(8.9%, 26.2%)	8 (10.4%)	(4.6%, 19.4%)
		Moderate problem	13 (16.3%)	(8.9%, 26.2%)	14 (18.2%)	(10.3%, 28.6%)
		Severe problem	7 (8.8%)	(3.6%, 17.2%)	7 (9.1%)	(3.7%, 17.8%)
		Problem as bad as it can be	5 (6.3%)	(2.1%, 14.0%)	5 (6.5%)	(2.1%, 14.5%)

*Confidence intervals calculated using Clopper-Pearson method

Table 14.39 SNOT-22 items change from baseline (Improved, No Change, Worsened) to Week 4, FAS

Parameter	Week	Change from baseline	Active N=81		Placebo N=79	
			n (%)	95% CI*	n (%)	95% CI*
Need to blow nose	Week 4	Improved	38 (47.5%)	(36.2%, 59.0%)	29 (37.7%)	(26.9%, 49.4%)
		No change	32 (40.0%)	(29.2%, 51.6%)	26 (33.8%)	(23.4%, 45.4%)
		Worsened	10 (12.5%)	(6.2%, 21.8%)	22 (28.6%)	(18.8%, 40.0%)
Sneezing	Week 4	Improved	29 (36.3%)	(25.8%, 47.8%)	27 (35.1%)	(24.5%, 46.8%)
		No change	39 (48.8%)	(37.4%, 60.2%)	35 (45.5%)	(34.1%, 57.2%)
		Worsened	12 (15.0%)	(8.0%, 24.7%)	15 (19.5%)	(11.3%, 30.1%)
Runny nose	Week 4	Improved	34 (42.5%)	(31.5%, 54.1%)	23 (29.9%)	(20.0%, 41.4%)
		No change	31 (38.8%)	(28.1%, 50.3%)	29 (37.7%)	(26.9%, 49.4%)
		Worsened	15 (18.8%)	(10.9%, 29.0%)	25 (32.5%)	(22.2%, 44.1%)
Blockage/congestion of nose	Week 4	Improved	41 (51.3%)	(39.8%, 62.6%)	28 (36.4%)	(25.7%, 48.1%)
		No change	31 (38.8%)	(28.1%, 50.3%)	36 (46.8%)	(35.3%, 58.5%)
		Worsened	8 (10.0%)	(4.4%, 18.8%)	13 (16.9%)	(9.3%, 27.1%)
Sense of smell/taste	Week 4	Improved	27 (33.8%)	(23.6%, 45.2%)	19 (24.7%)	(15.6%, 35.8%)
		No change	40 (50.0%)	(38.6%, 61.4%)	42 (54.5%)	(42.8%, 65.9%)
		Worsened	13 (16.3%)	(8.9%, 26.2%)	16 (20.8%)	(12.4%, 31.5%)
Cough	Week 4	Improved	21 (26.3%)	(17.0%, 37.3%)	16 (20.8%)	(12.4%, 31.5%)
		No change	46 (57.5%)	(45.9%, 68.5%)	41 (53.2%)	(41.5%, 64.7%)
		Worsened	13 (16.3%)	(8.9%, 26.2%)	20 (26.0%)	(16.6%, 37.2%)
Post-nasal discharge	Week 4	Improved	26 (32.5%)	(22.4%, 43.9%)	27 (35.1%)	(24.5%, 46.8%)
		No change	30 (37.5%)	(26.9%, 49.0%)	21 (27.3%)	(17.7%, 38.6%)
		Worsened	24 (30.0%)	(20.3%, 41.3%)	29 (37.7%)	(26.9%, 49.4%)
Thick nasal discharge	Week 4	Improved	30 (37.5%)	(26.9%, 49.0%)	24 (31.2%)	(21.1%, 42.7%)
		No change	38 (47.5%)	(36.2%, 59.0%)	34 (44.2%)	(32.8%, 55.9%)
		Worsened	12 (15.0%)	(8.0%, 24.7%)	19 (24.7%)	(15.6%, 35.8%)
Ear fullnes	Week 4	Improved	32 (40.0%)	(29.2%, 51.6%)	29 (37.7%)	(26.9%, 49.4%)
		No change	38 (47.5%)	(36.2%, 59.0%)	34 (44.2%)	(32.8%, 55.9%)
		Worsened	10 (12.5%)	(6.2%, 21.8%)	14 (18.2%)	(10.3%, 28.6%)
Dizziness	Week 4	Improved	21 (26.3%)	(17.0%, 37.3%)	17 (22.1%)	(13.4%, 33.0%)
		No change	47 (58.8%)	(47.2%, 69.6%)	44 (57.1%)	(45.4%, 68.4%)
		Worsened	12 (15.0%)	(8.0%, 24.7%)	16 (20.8%)	(12.4%, 31.5%)
Ear pain	Week 4	Improved	13 (16.3%)	(8.9%, 26.2%)	10 (13.0%)	(6.4%, 22.6%)
		No change	61 (76.3%)	(65.4%, 85.1%)	57 (74.0%)	(62.8%, 83.4%)
		Worsened	6 (7.5%)	(2.8%, 15.6%)	10 (13.0%)	(6.4%, 22.6%)
Facial pain/pressure	Week 4	Improved	19 (23.8%)	(14.9%, 34.6%)	16 (20.8%)	(12.4%, 31.5%)
		No change	53 (66.3%)	(54.8%, 76.4%)	53 (68.8%)	(57.3%, 78.9%)
		Worsened	8 (10.0%)	(4.4%, 18.8%)	8 (10.4%)	(4.6%, 19.4%)
Difficulty falling asleep	Week 4	Improved	31 (38.8%)	(28.1%, 50.3%)	18 (23.4%)	(14.5%, 34.4%)
		No change	33 (41.3%)	(30.4%, 52.8%)	39 (50.6%)	(39.0%, 62.2%)
		Worsened	16 (20.0%)	(11.9%, 30.4%)	20 (26.0%)	(16.6%, 37.2%)
Waking up at night	Week 4	Improved	31 (38.8%)	(28.1%, 50.3%)	25 (32.5%)	(22.2%, 44.1%)
		No change	30 (37.5%)	(26.9%, 49.0%)	31 (40.3%)	(29.2%, 52.1%)
		Worsened	19 (23.8%)	(14.9%, 34.6%)	21 (27.3%)	(17.7%, 38.6%)
Lack of good night's sleep	Week 4	Improved	35 (43.8%)	(32.7%, 55.3%)	24 (31.2%)	(21.1%, 42.7%)
		No change	26 (32.5%)	(22.4%, 43.9%)	37 (48.1%)	(36.5%, 59.7%)
		Worsened	19 (23.8%)	(14.9%, 34.6%)	16 (20.8%)	(12.4%, 31.5%)

Parameter	Week	Change from baseline	Active N=81 n (%)	Active N=81 95% CI*	Placebo N=79 n (%)	Placebo N=79 95% CI*
Waking up tired	Week 4	Improved	35 (43.8%)	(32.7%, 55.3%)	26 (33.8%)	(23.4%, 45.4%)
		No change	32 (40.0%)	(29.2%, 51.6%)	32 (41.6%)	(30.4%, 53.4%)
		Worsened	13 (16.3%)	(8.9%, 26.2%)	19 (24.7%)	(15.6%, 35.8%)
Fatigue	Week 4	Improved	34 (42.5%)	(31.5%, 54.1%)	28 (36.4%)	(25.7%, 48.1%)
		No change	32 (40.0%)	(29.2%, 51.6%)	26 (33.8%)	(23.4%, 45.4%)
		Worsened	14 (17.5%)	(9.9%, 27.6%)	23 (29.9%)	(20.0%, 41.4%)
Reduced productivity	Week 4	Improved	26 (32.5%)	(22.4%, 43.9%)	27 (35.1%)	(24.5%, 46.8%)
		No change	41 (51.3%)	(39.8%, 62.6%)	32 (41.6%)	(30.4%, 53.4%)
		Worsened	13 (16.3%)	(8.9%, 26.2%)	18 (23.4%)	(14.5%, 34.4%)
Reduced concentration	Week 4	Improved	30 (37.5%)	(26.9%, 49.0%)	25 (32.5%)	(22.2%, 44.1%)
		No change	33 (41.3%)	(30.4%, 52.8%)	38 (49.4%)	(37.8%, 61.0%)
		Worsened	17 (21.3%)	(12.9%, 31.8%)	14 (18.2%)	(10.3%, 28.6%)
Frustrated/restless/ irritable	Week 4	Improved	29 (36.3%)	(25.8%, 47.8%)	23 (29.9%)	(20.0%, 41.4%)
		No change	35 (43.8%)	(32.7%, 55.3%)	35 (45.5%)	(34.1%, 57.2%)
		Worsened	16 (20.0%)	(11.9%, 30.4%)	19 (24.7%)	(15.6%, 35.8%)
Sad	Week 4	Improved	18 (22.5%)	(13.9%, 33.2%)	18 (23.4%)	(14.5%, 34.4%)
		No change	45 (56.3%)	(44.7%, 67.3%)	50 (64.9%)	(53.2%, 75.5%)
		Worsened	17 (21.3%)	(12.9%, 31.8%)	9 (11.7%)	(5.5%, 21.0%)
Embarrassed	Week 4	Improved	36 (45.0%)	(33.8%, 56.5%)	31 (40.3%)	(29.2%, 52.1%)
		No change	28 (35.0%)	(24.7%, 46.5%)	25 (32.5%)	(22.2%, 44.1%)
		Worsened	16 (20.0%)	(11.9%, 30.4%)	21 (27.3%)	(17.7%, 38.6%)

*Confidence intervals calculated using Clopper-Pearson method

Table 14.40 SNOT-22 item reported as one of the five most significant problems at Screening and Week 4, FAS

Parameter	Visit	Active N=81 n (%)	Active N=81 95% CI*	Placebo N=79 n (%)	Placebo N=79 95% CI*
Need to blow nose	Screening	35 (43.2%)	(32.2%, 54.7%)	29 (36.7%)	(26.1%, 48.3%)
	Week 4	36 (45.0%)	(33.8%, 56.5%)	29 (37.7%)	(26.9%, 49.4%)
Sneezing	Screening	10 (12.3%)	(6.1%, 21.5%)	9 (11.4%)	(5.3%, 20.5%)
	Week 4	8 (10.0%)	(4.4%, 18.8%)	12 (15.6%)	(8.3%, 25.6%)
Runny nose	Screening	24 (29.6%)	(20.0%, 40.8%)	27 (34.2%)	(23.9%, 45.7%)
	Week 4	26 (32.5%)	(22.4%, 43.9%)	25 (32.5%)	(22.2%, 44.1%)
Blockage/congestion of nose	Screening	78 (96.3%)	(89.6%, 99.2%)	73 (92.4%)	(84.2%, 97.2%)
	Week 4	70 (87.5%)	(78.2%, 93.8%)	70 (90.9%)	(82.2%, 96.3%)
Sense of smell/taste	Screening	12 (14.8%)	(7.9%, 24.4%)	8 (10.1%)	(4.5%, 19.0%)
	Week 4	9 (11.3%)	(5.3%, 20.3%)	11 (14.3%)	(7.4%, 24.1%)
Cough	Screening	2 (2.5%)	(0.3%, 8.6%)	6 (7.6%)	(2.8%, 15.8%)
	Week 4	5 (6.3%)	(2.1%, 14.0%)	7 (9.1%)	(3.7%, 17.8%)
Post-nasal discharge	Screening	18 (22.2%)	(13.7%, 32.8%)	21 (26.6%)	(17.3%, 37.7%)
	Week 4	27 (33.8%)	(23.6%, 45.2%)	24 (31.2%)	(21.1%, 42.7%)
Thick nasal discharge	Screening	9 (11.1%)	(5.2%, 20.0%)	3 (3.8%)	(0.8%, 10.7%)
	Week 4	2 (2.5%)	(0.3%, 8.7%)	4 (5.2%)	(1.4%, 12.8%)

		Active N=81		Placebo N=79	
Parameter	**Visit**	**n (%)**	**95% CI***	**n (%)**	**95% CI***
Ear fullnes	Screening	13 (16.0%)	(8.8%, 25.9%)	11 (13.9%)	(7.2%, 23.5%)
	Week 4	9 (11.3%)	(5.3%, 20.3%)	5 (6.5%)	(2.1%, 14.5%)
Dizziness	Screening	4 (4.9%)	(1.4%, 12.2%)	1 (1.3%)	(0.0%, 6.9%)
	Week 4	5 (6.3%)	(2.1%, 14.0%)	2 (2.6%)	(0.3%, 9.1%)
Ear pain	Screening	1 (1.2%)	(0.0%, 6.7%)	2 (2.5%)	(0.3%, 8.8%)
	Week 4	2 (2.5%)	(0.3%, 8.7%)	2 (2.6%)	(0.3%, 9.1%)
Facial pain/pressure	Screening	6 (7.4%)	(2.8%, 15.4%)	9 (11.4%)	(5.3%, 20.5%)
	Week 4	7 (8.8%)	(3.6%, 17.2%)	6 (7.8%)	(2.9%, 16.2%)
Difficulty falling asleep	Screening	18 (22.2%)	(13.7%, 32.8%)	16 (20.3%)	(12.0%, 30.8%)
	Week 4	13 (16.3%)	(8.9%, 26.2%)	20 (26.0%)	(16.6%, 37.2%)
Waking up at night	Screening	25 (30.9%)	(21.1%, 42.1%)	27 (34.2%)	(23.9%, 45.7%)
	Week 4	24 (30.0%)	(20.3%, 41.3%)	30 (39.0%)	(28.0%, 50.8%)
Lack of good night's sleep	Screening	29 (35.8%)	(25.4%, 47.2%)	21 (26.6%)	(17.3%, 37.7%)
	Week 4	26 (32.5%)	(22.4%, 43.9%)	24 (31.2%)	(21.1%, 42.7%)
Waking up tired	Screening	27 (33.3%)	(23.2%, 44.7%)	33 (41.8%)	(30.8%, 53.4%)
	Week 4	25 (31.3%)	(21.3%, 42.6%)	31 (40.3%)	(29.2%, 52.1%)
Fatigue	Screening	18 (22.2%)	(13.7%, 32.8%)	20 (25.3%)	(16.2%, 36.4%)
	Week 4	20 (25.0%)	(16.0%, 35.9%)	19 (24.7%)	(15.6%, 35.8%)
Reduced productivity	Screening	4 (4.9%)	(1.4%, 12.2%)	1 (1.3%)	(0.0%, 6.9%)
	Week 4	8 (10.0%)	(4.4%, 18.8%)	1 (1.3%)	(0.0%, 7.0%)
Reduced concentration	Screening	6 (7.4%)	(2.8%, 15.4%)	2 (2.5%)	(0.3%, 8.8%)
	Week 4	6 (7.5%)	(2.8%, 15.6%)	2 (2.6%)	(0.3%, 9.1%)
Frustrated/restless/irritable	Screening	6 (7.4%)	(2.8%, 15.4%)	4 (5.1%)	(1.4%, 12.5%)
	Week 4	8 (10.0%)	(4.4%, 18.8%)	4 (5.2%)	(1.4%, 12.8%)
Sad	Screening	1 (1.2%)	(0.0%, 6.7%)	1 (1.3%)	(0.0%, 6.9%)
	Week 4	4 (5.0%)	(1.4%, 12.3%)	0	(0.0%, 4.7%)
Embarrassed	Screening	21 (25.9%)	(16.8%, 36.9%)	21 (26.6%)	(17.3%, 37.7%)
	Week 4	15 (18.8%)	(10.9%, 29.0%)	17 (22.1%)	(13.4%, 33.0%)

*Confidence intervals calculated using Clopper-Pearson method.

Table 14.41 SNOT-22 individual items at Weeks 8 and 24, FAS

			Active + Active N=81		Placebo + Active N=79	
Parameter	**Week**	**Score**	**n (%)**	**95% CI***	**n (%)**	**95% CI***
Need to blow nose	Week 8	No problem	11 (14.1%)	(7.3%, 23.8%)	10 (13.3%)	(6.6%, 23.2%)
		Very mild problem	23 (29.5%)	(19.7%, 40.9%)	16 (21.3%)	(12.7%, 32.3%)
		Mild or slight problem	17 (21.8%)	(13.2%, 32.6%)	20 (26.7%)	(17.1%, 38.1%)
		Moderate problem	17 (21.8%)	(13.2%, 32.6%)	11 (14.7%)	(7.6%, 24.7%)
		Severe problem	10 (12.8%)	(6.3%, 22.3%)	13 (17.3%)	(9.6%, 27.8%)
		Problem as bad as it can be	0	(0.0%, 4.6%)	5 (6.7%)	(2.2%, 14.9%)
	Week 24	No problem	10 (13.0%)	(6.4%, 22.6%)	9 (12.0%)	(5.6%, 21.6%)
		Very mild problem	21 (27.3%)	(17.7%, 38.6%)	25 (33.3%)	(22.9%, 45.2%)
		Mild or slight problem	9 (11.7%)	(5.5%, 21.0%)	17 (22.7%)	(13.8%, 33.8%)
		Moderate problem	18 (23.4%)	(14.5%, 34.4%)	10 (13.3%)	(6.6%, 23.2%)
		Severe problem	16 (20.8%)	(12.4%, 31.5%)	13 (17.3%)	(9.6%, 27.8%)
		Problem as bad as it can be	3 (3.9%)	(0.8%, 11.0%)	1 (1.3%)	(0.0%, 7.2%)
Sneezing	Week 8	No problem	24 (30.8%)	(20.8%, 42.2%)	18 (24.0%)	(14.9%, 35.3%)
		Very mild problem	25 (32.1%)	(21.9%, 43.6%)	29 (38.7%)	(27.6%, 50.6%)
		Mild or slight problem	15 (19.2%)	(11.2%, 29.7%)	14 (18.7%)	(10.6%, 29.3%)
		Moderate problem	12 (15.4%)	(8.2%, 25.3%)	12 (16.0%)	(8.6%, 26.3%)
		Severe problem	2 (2.6%)	(0.3%, 9.0%)	2 (2.7%)	(0.3%, 9.3%)
		Problem as bad as it can be	0	(0.0%, 4.6%)	0	(0.0%, 4.8%)
	Week 24	No problem	22 (28.6%)	(18.8%, 40.0%)	23 (30.7%)	(20.5%, 42.4%)
		Very mild problem	29 (37.7%)	(26.9%, 49.4%)	32 (42.7%)	(31.3%, 54.6%)
		Mild or slight problem	11 (14.3%)	(7.4%, 24.1%)	11 (14.7%)	(7.6%, 24.7%)
		Moderate problem	12 (15.6%)	(8.3%, 25.6%)	4 (5.3%)	(1.5%, 13.1%)
		Severe problem	2 (2.6%)	(0.3%, 9.1%)	5 (6.7%)	(2.2%, 14.9%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 7.0%)	0	(0.0%, 4.8%)
Runny nose	Week 8	No problem	22 (28.2%)	(18.6%, 39.5%)	13 (17.3%)	(9.6%, 27.8%)
		Very mild problem	22 (28.2%)	(18.6%, 39.5%)	22 (29.3%)	(19.4%, 41.0%)
		Mild or slight problem	18 (23.1%)	(14.3%, 34.0%)	17 (22.7%)	(13.8%, 33.8%)
		Moderate problem	10 (12.8%)	(6.3%, 22.3%)	6 (8.0%)	(3.0%, 16.6%)
		Severe problem	5 (6.4%)	(2.1%, 14.3%)	16 (21.3%)	(12.7%, 32.3%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 6.9%)	1 (1.3%)	(0.0%, 7.2%)
	Week 24	No problem	19 (24.7%)	(15.6%, 35.8%)	22 (29.3%)	(19.4%, 41.0%)
		Very mild problem	19 (24.7%)	(15.6%, 35.8%)	21 (28.0%)	(18.2%, 39.6%)
		Mild or slight problem	14 (18.2%)	(10.3%, 28.6%)	15 (20.0%)	(11.6%, 30.8%)
		Moderate problem	10 (13.0%)	(6.4%, 22.6%)	7 (9.3%)	(3.8%, 18.3%)
		Severe problem	10 (13.0%)	(6.4%, 22.6%)	5 (6.7%)	(2.2%, 14.9%)
		Problem as bad as it can be	5 (6.5%)	(2.1%, 14.5%)	5 (6.7%)	(2.2%, 14.9%)
Blockage/congestion of nose	Week 8	No problem	3 (3.8%)	(0.8%, 10.8%)	2 (2.7%)	(0.3%, 9.3%)
		Very mild problem	9 (11.5%)	(5.4%, 20.8%)	5 (6.7%)	(2.2%, 14.9%)
		Mild or slight problem	13 (16.7%)	(9.2%, 26.8%)	13 (17.3%)	(9.6%, 27.8%)
		Moderate problem	26 (33.3%)	(23.1%, 44.9%)	13 (17.3%)	(9.6%, 27.8%)
		Severe problem	20 (25.6%)	(16.4%, 36.8%)	32 (42.7%)	(31.3%, 54.6%)
		Problem as bad as it can be	7 (9.0%)	(3.7%, 17.6%)	10 (13.3%)	(6.6%, 23.2%)

Parameter	Week	Score	Active + Active N=81		Placebo + Active N=79	
			n (%)	95% CI*	n (%)	95% CI*
	Week 24	No problem	2 (2.6%)	(0.3%, 9.1%)	4 (5.3%)	(1.5%, 13.1%)
		Very mild problem	9 (11.7%)	(5.5%, 21.0%)	10 (13.3%)	(6.6%, 23.2%)
		Mild or slight problem	10 (13.0%)	(6.4%, 22.6%)	9 (12.0%)	(5.6%, 21.6%)
		Moderate problem	19 (24.7%)	(15.6%, 35.8%)	18 (24.0%)	(14.9%, 35.3%)
		Severe problem	24 (31.2%)	(21.1%, 42.7%)	20 (26.7%)	(17.1%, 38.1%)
		Problem as bad as it can be	13 (16.9%)	(9.3%, 27.1%)	14 (18.7%)	(10.6%, 29.3%)
Sense of smell/taste	Week 8	No problem	42 (53.8%)	(42.2%, 65.2%)	36 (48.0%)	(36.3%, 59.8%)
		Very mild problem	15 (19.2%)	(11.2%, 29.7%)	17 (22.7%)	(13.8%, 33.8%)
		Mild or slight problem	4 (5.1%)	(1.4%, 12.6%)	10 (13.3%)	(6.6%, 23.2%)
		Moderate problem	9 (11.5%)	(5.4%, 20.8%)	8 (10.7%)	(4.7%, 19.9%)
		Severe problem	5 (6.4%)	(2.1%, 14.3%)	3 (4.0%)	(0.8%, 11.2%)
		Problem as bad as it can be	3 (3.8%)	(0.8%, 10.8%)	1 (1.3%)	(0.0%, 7.2%)
	Week 24	No problem	31 (40.3%)	(29.2%, 52.1%)	43 (57.3%)	(45.4%, 68.7%)
		Very mild problem	18 (23.4%)	(14.5%, 34.4%)	9 (12.0%)	(5.6%, 21.6%)
		Mild or slight problem	13 (16.9%)	(9.3%, 27.1%)	11 (14.7%)	(7.6%, 24.7%)
		Moderate problem	5 (6.5%)	(2.1%, 14.5%)	6 (8.0%)	(3.0%, 16.6%)
		Severe problem	6 (7.8%)	(2.9%, 16.2%)	5 (6.7%)	(2.2%, 14.9%)
		Problem as bad as it can be	4 (5.2%)	(1.4%, 12.8%)	1 (1.3%)	(0.0%, 7.2%)
Cough	Week 8	No problem	49 (62.8%)	(51.1%, 73.5%)	41 (54.7%)	(42.7%, 66.2%)
		Very mild problem	21 (26.9%)	(17.5%, 38.2%)	19 (25.3%)	(16.0%, 36.7%)
		Mild or slight problem	2 (2.6%)	(0.3%, 9.0%)	9 (12.0%)	(5.6%, 21.6%)
		Moderate problem	3 (3.8%)	(0.8%, 10.8%)	4 (5.3%)	(1.5%, 13.1%)
		Severe problem	3 (3.8%)	(0.8%, 10.8%)	2 (2.7%)	(0.3%, 9.3%)
		Problem as bad as it can be	0	(0.0%, 4.6%)	0	(0.0%, 4.8%)
	Week 24	No problem	42 (54.5%)	(42.8%, 65.9%)	38 (50.7%)	(38.9%, 62.4%)
		Very mild problem	18 (23.4%)	(14.5%, 34.4%)	27 (36.0%)	(25.2%, 47.9%)
		Mild or slight problem	11 (14.3%)	(7.4%, 24.1%)	6 (8.0%)	(3.0%, 16.6%)
		Moderate problem	2 (2.6%)	(0.3%, 9.1%)	3 (4.0%)	(0.8%, 11.2%)
		Severe problem	2 (2.6%)	(0.3%, 9.1%)	1 (1.3%)	(0.0%, 7.2%)
		Problem as bad as it can be	2 (2.6%)	(0.3%, 9.1%)	0	(0.0%, 4.8%)
Post-nasal discharge	Week 8	No problem	29 (37.2%)	(26.5%, 48.9%)	18 (24.0%)	(14.9%, 35.3%)
		Very mild problem	14 (17.9%)	(10.2%, 28.3%)	14 (18.7%)	(10.6%, 29.3%)
		Mild or slight problem	16 (20.5%)	(12.2%, 31.2%)	16 (21.3%)	(12.7%, 32.3%)
		Moderate problem	11 (14.1%)	(7.3%, 23.8%)	15 (20.0%)	(11.6%, 30.8%)
		Severe problem	5 (6.4%)	(2.1%, 14.3%)	6 (8.0%)	(3.0%, 16.6%)
		Problem as bad as it can be	3 (3.8%)	(0.8%, 10.8%)	6 (8.0%)	(3.0%, 16.6%)

Parameter	Week	Score	Active + Active N=81		Placebo + Active N=79	
			n (%)	95% CI*	n (%)	95% CI*
	Week 24	No problem	24 (31.2%)	(21.1%, 42.7%)	25 (33.3%)	(22.9%, 45.2%)
		Very mild problem	12 (15.6%)	(8.3%, 25.6%)	12 (16.0%)	(8.6%, 26.3%)
		Mild or slight problem	17 (22.1%)	(13.4%, 33.0%)	16 (21.3%)	(12.7%, 32.3%)
		Moderate problem	13 (16.9%)	(9.3%, 27.1%)	14 (18.7%)	(10.6%, 29.3%)
		Severe problem	7 (9.1%)	(3.7%, 17.8%)	5 (6.7%)	(2.2%, 14.9%)
		Problem as bad as it can be	4 (5.2%)	(1.4%, 12.8%)	3 (4.0%)	(0.8%, 11.2%)
Thick nasal discharge	Week 8	No problem	45 (57.7%)	(46.0%, 68.8%)	40 (53.3%)	(41.4%, 64.9%)
		Very mild problem	16 (20.5%)	(12.2%, 31.2%)	13 (17.3%)	(9.6%, 27.8%)
		Mild or slight problem	8 (10.3%)	(4.5%, 19.2%)	12 (16.0%)	(8.6%, 26.3%)
		Moderate problem	7 (9.0%)	(3.7%, 17.6%)	6 (8.0%)	(3.0%, 16.6%)
		Severe problem	2 (2.6%)	(0.3%, 9.0%)	4 (5.3%)	(1.5%, 13.1%)
		Problem as bad as it can be	0	(0.0%, 4.6%)	0	(0.0%, 4.8%)
	Week 24	No problem	43 (55.8%)	(44.1%, 67.2%)	39 (52.0%)	(40.2%, 63.7%)
		Very mild problem	7 (9.1%)	(3.7%, 17.8%)	21 (28.0%)	(18.2%, 39.6%)
		Mild or slight problem	13 (16.9%)	(9.3%, 27.1%)	4 (5.3%)	(1.5%, 13.1%)
		Moderate problem	7 (9.1%)	(3.7%, 17.8%)	8 (10.7%)	(4.7%, 19.9%)
		Severe problem	6 (7.8%)	(2.9%, 16.2%)	3 (4.0%)	(0.8%, 11.2%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 7.0%)	0	(0.0%, 4.8%)
Ear fullnes	Week 8	No problem	40 (51.3%)	(39.7%, 62.8%)	44 (58.7%)	(46.7%, 69.9%)
		Very mild problem	16 (20.5%)	(12.2%, 31.2%)	16 (21.3%)	(12.7%, 32.3%)
		Mild or slight problem	11 (14.1%)	(7.3%, 23.8%)	6 (8.0%)	(3.0%, 16.6%)
		Moderate problem	7 (9.0%)	(3.7%, 17.6%)	2 (2.7%)	(0.3%, 9.3%)
		Severe problem	4 (5.1%)	(1.4%, 12.6%)	5 (6.7%)	(2.2%, 14.9%)
		Problem as bad as it can be	0	(0.0%, 4.6%)	2 (2.7%)	(0.3%, 9.3%)
	Week 24	No problem	38 (49.4%)	(37.8%, 61.0%)	45 (60.0%)	(48.0%, 71.1%)
		Very mild problem	15 (19.5%)	(11.3%, 30.1%)	10 (13.3%)	(6.6%, 23.2%)
		Mild or slight problem	11 (14.3%)	(7.4%, 24.1%)	8 (10.7%)	(4.7%, 19.9%)
		Moderate problem	7 (9.1%)	(3.7%, 17.8%)	5 (6.7%)	(2.2%, 14.9%)
		Severe problem	6 (7.8%)	(2.9%, 16.2%)	7 (9.3%)	(3.8%, 18.3%)
		Problem as bad as it can be	0	(0.0%, 4.7%)	0	(0.0%, 4.8%)
Dizziness	Week 8	No problem	60 (76.9%)	(66.0%, 85.7%)	47 (62.7%)	(50.7%, 73.6%)
		Very mild problem	11 (14.1%)	(7.3%, 23.8%)	17 (22.7%)	(13.8%, 33.8%)
		Mild or slight problem	4 (5.1%)	(1.4%, 12.6%)	5 (6.7%)	(2.2%, 14.9%)
		Moderate problem	1 (1.3%)	(0.0%, 6.9%)	4 (5.3%)	(1.5%, 13.1%)
		Severe problem	2 (2.6%)	(0.3%, 9.0%)	0	(0.0%, 4.8%)
		Problem as bad as it can be	0	(0.0%, 4.6%)	2 (2.7%)	(0.3%, 9.3%)

Parameter	Week	Score	Active + Active N=81		Placebo + Active N=79	
			n (%)	95% CI*	n (%)	95% CI*
	Week 24	No problem	53 (68.8%)	(57.3%, 78.9%)	53 (70.7%)	(59.0%, 80.6%)
		Very mild problem	13 (16.9%)	(9.3%, 27.1%)	9 (12.0%)	(5.6%, 21.6%)
		Mild or slight problem	6 (7.8%)	(2.9%, 16.2%)	9 (12.0%)	(5.6%, 21.6%)
		Moderate problem	2 (2.6%)	(0.3%, 9.1%)	4 (5.3%)	(1.5%, 13.1%)
		Severe problem	3 (3.9%)	(0.8%, 11.0%)	0	(0.0%, 4.8%)
		Problem as bad as it can be	0	(0.0%, 4.7%)	0	(0.0%, 4.8%)
Ear pain	Week 8	No problem	60 (76.9%)	(66.0%, 85.7%)	65 (86.7%)	(76.8%, 93.4%)
		Very mild problem	13 (16.7%)	(9.2%, 26.8%)	5 (6.7%)	(2.2%, 14.9%)
		Mild or slight problem	3 (3.8%)	(0.8%, 10.8%)	1 (1.3%)	(0.0%, 7.2%)
		Moderate problem	2 (2.6%)	(0.3%, 9.0%)	2 (2.7%)	(0.3%, 9.3%)
		Severe problem	0	(0.0%, 4.6%)	1 (1.3%)	(0.0%, 7.2%)
		Problem as bad as it can be	0	(0.0%, 4.6%)	1 (1.3%)	(0.0%, 7.2%)
	Week 24	No problem	57 (74.0%)	(62.8%, 83.4%)	58 (77.3%)	(66.2%, 86.2%)
		Very mild problem	16 (20.8%)	(12.4%, 31.5%)	7 (9.3%)	(3.8%, 18.3%)
		Mild or slight problem	2 (2.6%)	(0.3%, 9.1%)	6 (8.0%)	(3.0%, 16.6%)
		Moderate problem	1 (1.3%)	(0.0%, 7.0%)	4 (5.3%)	(1.5%, 13.1%)
		Severe problem	1 (1.3%)	(0.0%, 7.0%)	0	(0.0%, 4.8%)
		Problem as bad as it can be	0	(0.0%, 4.7%)	0	(0.0%, 4.8%)
Facial pain/pressure	Week 8	No problem	53 (67.9%)	(56.4%, 78.1%)	49 (65.3%)	(53.5%, 76.0%)
		Very mild problem	11 (14.1%)	(7.3%, 23.8%)	13 (17.3%)	(9.6%, 27.8%)
		Mild or slight problem	5 (6.4%)	(2.1%, 14.3%)	6 (8.0%)	(3.0%, 16.6%)
		Moderate problem	2 (2.6%)	(0.3%, 9.0%)	2 (2.7%)	(0.3%, 9.3%)
		Severe problem	6 (7.7%)	(2.9%, 16.0%)	4 (5.3%)	(1.5%, 13.1%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 6.9%)	1 (1.3%)	(0.0%, 7.2%)
	Week 24	No problem	46 (59.7%)	(47.9%, 70.8%)	53 (70.7%)	(59.0%, 80.6%)
		Very mild problem	17 (22.1%)	(13.4%, 33.0%)	11 (14.7%)	(7.6%, 24.7%)
		Mild or slight problem	5 (6.5%)	(2.1%, 14.5%)	4 (5.3%)	(1.5%, 13.1%)
		Moderate problem	5 (6.5%)	(2.1%, 14.5%)	4 (5.3%)	(1.5%, 13.1%)
		Severe problem	1 (1.3%)	(0.0%, 7.0%)	2 (2.7%)	(0.3%, 9.3%)
		Problem as bad as it can be	3 (3.9%)	(0.8%, 11.0%)	1 (1.3%)	(0.0%, 7.2%)
Difficulty falling asleep	Week 8	No problem	32 (41.0%)	(30.0%, 52.7%)	29 (38.7%)	(27.6%, 50.6%)
		Very mild problem	10 (12.8%)	(6.3%, 22.3%)	17 (22.7%)	(13.8%, 33.8%)
		Mild or slight problem	15 (19.2%)	(11.2%, 29.7%)	12 (16.0%)	(8.6%, 26.3%)
		Moderate problem	17 (21.8%)	(13.2%, 32.6%)	6 (8.0%)	(3.0%, 16.6%)
		Severe problem	3 (3.8%)	(0.8%, 10.8%)	7 (9.3%)	(3.8%, 18.3%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 6.9%)	4 (5.3%)	(1.5%, 13.1%)

Parameter	Week	Score	Active + Active N=81		Placebo + Active N=79	
			n (%)	95% CI*	n (%)	95% CI*
	Week 24	No problem	35 (45.5%)	(34.1%, 57.2%)	35 (46.7%)	(35.1%, 58.6%)
		Very mild problem	10 (13.0%)	(6.4%, 22.6%)	13 (17.3%)	(9.6%, 27.8%)
		Mild or slight problem	14 (18.2%)	(10.3%, 28.6%)	11 (14.7%)	(7.6%, 24.7%)
		Moderate problem	10 (13.0%)	(6.4%, 22.6%)	7 (9.3%)	(3.8%, 18.3%)
		Severe problem	6 (7.8%)	(2.9%, 16.2%)	7 (9.3%)	(3.8%, 18.3%)
		Problem as bad as it can be	2 (2.6%)	(0.3%, 9.1%)	2 (2.7%)	(0.3%, 9.3%)
Waking up at night	Week 8	No problem	18 (23.1%)	(14.3%, 34.0%)	15 (20.0%)	(11.6%, 30.8%)
		Very mild problem	12 (15.4%)	(8.2%, 25.3%)	13 (17.3%)	(9.6%, 27.8%)
		Mild or slight problem	21 (26.9%)	(17.5%, 38.2%)	16 (21.3%)	(12.7%, 32.3%)
		Moderate problem	16 (20.5%)	(12.2%, 31.2%)	17 (22.7%)	(13.8%, 33.8%)
		Severe problem	10 (12.8%)	(6.3%, 22.3%)	10 (13.3%)	(6.6%, 23.2%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 6.9%)	4 (5.3%)	(1.5%, 13.1%)
	Week 24	No problem	20 (26.0%)	(16.6%, 37.2%)	20 (26.7%)	(17.1%, 38.1%)
		Very mild problem	17 (22.1%)	(13.4%, 33.0%)	18 (24.0%)	(14.9%, 35.3%)
		Mild or slight problem	12 (15.6%)	(8.3%, 25.6%)	9 (12.0%)	(5.6%, 21.6%)
		Moderate problem	18 (23.4%)	(14.5%, 34.4%)	19 (25.3%)	(16.0%, 36.7%)
		Severe problem	5 (6.5%)	(2.1%, 14.5%)	6 (8.0%)	(3.0%, 16.6%)
		Problem as bad as it can be	5 (6.5%)	(2.1%, 14.5%)	3 (4.0%)	(0.8%, 11.2%)
Lack of good night's sleep	Week 8	No problem	18 (23.1%)	(14.3%, 34.0%)	19 (25.3%)	(16.0%, 36.7%)
		Very mild problem	21 (26.9%)	(17.5%, 38.2%)	12 (16.0%)	(8.6%, 26.3%)
		Mild or slight problem	14 (17.9%)	(10.2%, 28.3%)	17 (22.7%)	(13.8%, 33.8%)
		Moderate problem	13 (16.7%)	(9.2%, 26.8%)	13 (17.3%)	(9.6%, 27.8%)
		Severe problem	10 (12.8%)	(6.3%, 22.3%)	11 (14.7%)	(7.6%, 24.7%)
		Problem as bad as it can be	2 (2.6%)	(0.3%, 9.0%)	3 (4.0%)	(0.8%, 11.2%)
	Week 24	No problem	18 (23.4%)	(14.5%, 34.4%)	27 (36.0%)	(25.2%, 47.9%)
		Very mild problem	20 (26.0%)	(16.6%, 37.2%)	10 (13.3%)	(6.6%, 23.2%)
		Mild or slight problem	12 (15.6%)	(8.3%, 25.6%)	16 (21.3%)	(12.7%, 32.3%)
		Moderate problem	14 (18.2%)	(10.3%, 28.6%)	16 (21.3%)	(12.7%, 32.3%)
		Severe problem	9 (11.7%)	(5.5%, 21.0%)	6 (8.0%)	(3.0%, 16.6%)
		Problem as bad as it can be	4 (5.2%)	(1.4%, 12.8%)	0	(0.0%, 4.8%)
Waking up tired	Week 8	No problem	17 (21.8%)	(13.2%, 32.6%)	13 (17.3%)	(9.6%, 27.8%)
		Very mild problem	15 (19.2%)	(11.2%, 29.7%)	12 (16.0%)	(8.6%, 26.3%)
		Mild or slight problem	15 (19.2%)	(11.2%, 29.7%)	13 (17.3%)	(9.6%, 27.8%)
		Moderate problem	15 (19.2%)	(11.2%, 29.7%)	16 (21.3%)	(12.7%, 32.3%)
		Severe problem	13 (16.7%)	(9.2%, 26.8%)	15 (20.0%)	(11.6%, 30.8%)
		Problem as bad as it can be	3 (3.8%)	(0.8%, 10.8%)	6 (8.0%)	(3.0%, 16.6%)

Parameter	Week	Score	Active + Active N=81		Placebo + Active N=79	
			n (%)	95% CI*	n (%)	95% CI*
	Week 24	No problem	15 (19.5%)	(11.3%, 30.1%)	16 (21.3%)	(12.7%, 32.3%)
		Very mild problem	14 (18.2%)	(10.3%, 28.6%)	8 (10.7%)	(4.7%, 19.9%)
		Mild or slight problem	21 (27.3%)	(17.7%, 38.6%)	23 (30.7%)	(20.5%, 42.4%)
		Moderate problem	10 (13.0%)	(6.4%, 22.6%)	14 (18.7%)	(10.6%, 29.3%)
		Severe problem	12 (15.6%)	(8.3%, 25.6%)	9 (12.0%)	(5.6%, 21.6%)
		Problem as bad as it can be	5 (6.5%)	(2.1%, 14.5%)	5 (6.7%)	(2.2%, 14.9%)
Fatigue	Week 8	No problem	25 (32.1%)	(21.9%, 43.6%)	16 (21.3%)	(12.7%, 32.3%)
		Very mild problem	17 (21.8%)	(13.2%, 32.6%)	17 (22.7%)	(13.8%, 33.8%)
		Mild or slight problem	17 (21.8%)	(13.2%, 32.6%)	20 (26.7%)	(17.1%, 38.1%)
		Moderate problem	9 (11.5%)	(5.4%, 20.8%)	13 (17.3%)	(9.6%, 27.8%)
		Severe problem	9 (11.5%)	(5.4%, 20.8%)	8 (10.7%)	(4.7%, 19.9%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 6.9%)	1 (1.3%)	(0.0%, 7.2%)
	Week 24	No problem	20 (26.0%)	(16.6%, 37.2%)	22 (29.3%)	(19.4%, 41.0%)
		Very mild problem	22 (28.6%)	(18.8%, 40.0%)	18 (24.0%)	(14.9%, 35.3%)
		Mild or slight problem	12 (15.6%)	(8.3%, 25.6%)	15 (20.0%)	(11.6%, 30.8%)
		Moderate problem	13 (16.9%)	(9.3%, 27.1%)	11 (14.7%)	(7.6%, 24.7%)
		Severe problem	7 (9.1%)	(3.7%, 17.8%)	8 (10.7%)	(4.7%, 19.9%)
		Problem as bad as it can be	3 (3.9%)	(0.8%, 11.0%)	1 (1.3%)	(0.0%, 7.2%)
Reduced productivity	Week 8	No problem	36 (46.2%)	(34.8%, 57.8%)	32 (42.7%)	(31.3%, 54.6%)
		Very mild problem	13 (16.7%)	(9.2%, 26.8%)	17 (22.7%)	(13.8%, 33.8%)
		Mild or slight problem	16 (20.5%)	(12.2%, 31.2%)	16 (21.3%)	(12.7%, 32.3%)
		Moderate problem	10 (12.8%)	(6.3%, 22.3%)	7 (9.3%)	(3.8%, 18.3%)
		Severe problem	2 (2.6%)	(0.3%, 9.0%)	3 (4.0%)	(0.8%, 11.2%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 6.9%)	0	(0.0%, 4.8%)
	Week 24	No problem	31 (40.3%)	(29.2%, 52.1%)	38 (50.7%)	(38.9%, 62.4%)
		Very mild problem	16 (20.8%)	(12.4%, 31.5%)	12 (16.0%)	(8.6%, 26.3%)
		Mild or slight problem	15 (19.5%)	(11.3%, 30.1%)	13 (17.3%)	(9.6%, 27.8%)
		Moderate problem	10 (13.0%)	(6.4%, 22.6%)	10 (13.3%)	(6.6%, 23.2%)
		Severe problem	3 (3.9%)	(0.8%, 11.0%)	2 (2.7%)	(0.3%, 9.3%)
		Problem as bad as it can be	2 (2.6%)	(0.3%, 9.1%)	0	(0.0%, 4.8%)
Reduced concentration	Week 8	No problem	41 (52.6%)	(40.9%, 64.0%)	32 (42.7%)	(31.3%, 54.6%)
		Very mild problem	13 (16.7%)	(9.2%, 26.8%)	16 (21.3%)	(12.7%, 32.3%)
		Mild or slight problem	14 (17.9%)	(10.2%, 28.3%)	16 (21.3%)	(12.7%, 32.3%)
		Moderate problem	3 (3.8%)	(0.8%, 10.8%)	7 (9.3%)	(3.8%, 18.3%)
		Severe problem	6 (7.7%)	(2.9%, 16.0%)	4 (5.3%)	(1.5%, 13.1%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 6.9%)	0	(0.0%, 4.8%)

Parameter	Week	Score	Active + Active N=81		Placebo + Active N=79	
			n (%)	95% CI*	n (%)	95% CI*
	Week 24	No problem	34 (44.2%)	(32.8%, 55.9%)	39 (52.0%)	(40.2%, 63.7%)
		Very mild problem	16 (20.8%)	(12.4%, 31.5%)	10 (13.3%)	(6.6%, 23.2%)
		Mild or slight problem	12 (15.6%)	(8.3%, 25.6%)	15 (20.0%)	(11.6%, 30.8%)
		Moderate problem	10 (13.0%)	(6.4%, 22.6%)	9 (12.0%)	(5.6%, 21.6%)
		Severe problem	3 (3.9%)	(0.8%, 11.0%)	1 (1.3%)	(0.0%, 7.2%)
		Problem as bad as it can be	2 (2.6%)	(0.3%, 9.1%)	1 (1.3%)	(0.0%, 7.2%)
Frustrated/restless/irritable	Week 8	No problem	34 (43.6%)	(32.4%, 55.3%)	27 (36.0%)	(25.2%, 47.9%)
		Very mild problem	16 (20.5%)	(12.2%, 31.2%)	17 (22.7%)	(13.8%, 33.8%)
		Mild or slight problem	16 (20.5%)	(12.2%, 31.2%)	15 (20.0%)	(11.6%, 30.8%)
		Moderate problem	6 (7.7%)	(2.9%, 16.0%)	8 (10.7%)	(4.7%, 19.9%)
		Severe problem	5 (6.4%)	(2.1%, 14.3%)	6 (8.0%)	(3.0%, 16.6%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 6.9%)	2 (2.7%)	(0.3%, 9.3%)
	Week 24	No problem	36 (46.8%)	(35.3%, 58.5%)	39 (52.0%)	(40.2%, 63.7%)
		Very mild problem	15 (19.5%)	(11.3%, 30.1%)	8 (10.7%)	(4.7%, 19.9%)
		Mild or slight problem	9 (11.7%)	(5.5%, 21.0%)	15 (20.0%)	(11.6%, 30.8%)
		Moderate problem	12 (15.6%)	(8.3%, 25.6%)	9 (12.0%)	(5.6%, 21.6%)
		Severe problem	3 (3.9%)	(0.8%, 11.0%)	3 (4.0%)	(0.8%, 11.2%)
		Problem as bad as it can be	2 (2.6%)	(0.3%, 9.1%)	1 (1.3%)	(0.0%, 7.2%)
Sad	Week 8	No problem	49 (62.8%)	(51.1%, 73.5%)	42 (56.0%)	(44.1%, 67.5%)
		Very mild problem	9 (11.5%)	(5.4%, 20.8%)	21 (28.0%)	(18.2%, 39.6%)
		Mild or slight problem	12 (15.4%)	(8.2%, 25.3%)	10 (13.3%)	(6.6%, 23.2%)
		Moderate problem	5 (6.4%)	(2.1%, 14.3%)	1 (1.3%)	(0.0%, 7.2%)
		Severe problem	3 (3.8%)	(0.8%, 10.8%)	1 (1.3%)	(0.0%, 7.2%)
		Problem as bad as it can be	0	(0.0%, 4.6%)	0	(0.0%, 4.8%)
	Week 24	No problem	48 (62.3%)	(50.6%, 73.1%)	52 (69.3%)	(57.6%, 79.5%)
		Very mild problem	12 (15.6%)	(8.3%, 25.6%)	13 (17.3%)	(9.6%, 27.8%)
		Mild or slight problem	9 (11.7%)	(5.5%, 21.0%)	8 (10.7%)	(4.7%, 19.9%)
		Moderate problem	4 (5.2%)	(1.4%, 12.8%)	2 (2.7%)	(0.3%, 9.3%)
		Severe problem	3 (3.9%)	(0.8%, 11.0%)	0	(0.0%, 4.8%)
		Problem as bad as it can be	1 (1.3%)	(0.0%, 7.0%)	0	(0.0%, 4.8%)
Embarrassed	Week 8	No problem	38 (48.7%)	(37.2%, 60.3%)	28 (37.3%)	(26.4%, 49.3%)
		Very mild problem	6 (7.7%)	(2.9%, 16.0%)	12 (16.0%)	(8.6%, 26.3%)
		Mild or slight problem	16 (20.5%)	(12.2%, 31.2%)	8 (10.7%)	(4.7%, 19.9%)
		Moderate problem	11 (14.1%)	(7.3%, 23.8%)	12 (16.0%)	(8.6%, 26.3%)
		Severe problem	5 (6.4%)	(2.1%, 14.3%)	13 (17.3%)	(9.6%, 27.8%)
		Problem as bad as it can be	2 (2.6%)	(0.3%, 9.0%)	2 (2.7%)	(0.3%, 9.3%)
	Week 24	No problem	35 (45.5%)	(34.1%, 57.2%)	33 (44.0%)	(32.5%, 55.9%)
		Very mild problem	12 (15.6%)	(8.3%, 25.6%)	12 (16.0%)	(8.6%, 26.3%)
		Mild or slight problem	4 (5.2%)	(1.4%, 12.8%)	8 (10.7%)	(4.7%, 19.9%)
		Moderate problem	9 (11.7%)	(5.5%, 21.0%)	10 (13.3%)	(6.6%, 23.2%)
		Severe problem	11 (14.3%)	(7.4%, 24.1%)	6 (8.0%)	(3.0%, 16.6%)
		Problem as bad as it can be	6 (7.8%)	(2.9%, 16.2%)	6 (8.0%)	(3.0%, 16.6%)

*Confidence intervals calculated using Clopper-Pearson method

Table 14.42 SNOT-22 items change from baseline to Week 8 and 24, FAS

Parameter	Visit	Change from baseline	Active + Active N=81		Placebo + Active N=79	
			n (%)	95% CI*	n (%)	95% CI*
Need to blow nose	Week 8	Improved	48 (61.5%)	(49.8%, 72.3%)	31 (41.3%)	(30.1%, 53.3%)
		No change	21 (26.9%)	(17.5%, 38.2%)	22 (29.3%)	(19.4%, 41.0%)
		Worsened	9 (11.5%)	(5.4%, 20.8%)	22 (29.3%)	(19.4%, 41.0%)
	Week 24	Improved	37 (48.1%)	(36.5%, 59.7%)	42 (56.0%)	(44.1%, 67.5%)
		No change	31 (40.3%)	(29.2%, 52.1%)	19 (25.3%)	(16.0%, 36.7%)
		Worsened	9 (11.7%)	(5.5%, 21.0%)	14 (18.7%)	(10.6%, 29.3%)
Sneezing	Week 8	Improved	34 (43.6%)	(32.4%, 55.3%)	34 (45.3%)	(33.8%, 57.3%)
		No change	31 (39.7%)	(28.8%, 51.5%)	24 (32.0%)	(21.7%, 43.8%)
		Worsened	13 (16.7%)	(9.2%, 26.8%)	17 (22.7%)	(13.8%, 33.8%)
	Week 24	Improved	32 (41.6%)	(30.4%, 53.4%)	35 (46.7%)	(35.1%, 58.6%)
		No change	32 (41.6%)	(30.4%, 53.4%)	28 (37.3%)	(26.4%, 49.3%)
		Worsened	13 (16.9%)	(9.3%, 27.1%)	12 (16.0%)	(8.6%, 26.3%)
Runny nose	Week 8	Improved	36 (46.2%)	(34.8%, 57.8%)	29 (38.7%)	(27.6%, 50.6%)
		No change	28 (35.9%)	(25.3%, 47.6%)	25 (33.3%)	(22.9%, 45.2%)
		Worsened	14 (17.9%)	(10.2%, 28.3%)	21 (28.0%)	(18.2%, 39.6%)
	Week 24	Improved	28 (36.4%)	(25.7%, 48.1%)	37 (49.3%)	(37.6%, 61.1%)
		No change	33 (42.9%)	(31.6%, 54.6%)	19 (25.3%)	(16.0%, 36.7%)
		Worsened	16 (20.8%)	(12.4%, 31.5%)	19 (25.3%)	(16.0%, 36.7%)
Blockage/congestion of nose	Week 8	Improved	46 (59.0%)	(47.3%, 70.0%)	39 (52.0%)	(40.2%, 63.7%)
		No change	26 (33.3%)	(23.1%, 44.9%)	30 (40.0%)	(28.9%, 52.0%)
		Worsened	6 (7.7%)	(2.9%, 16.0%)	6 (8.0%)	(3.0%, 16.6%)
	Week 24	Improved	40 (51.9%)	(40.3%, 63.5%)	41 (54.7%)	(42.7%, 66.2%)
		No change	30 (39.0%)	(28.0%, 50.8%)	24 (32.0%)	(21.7%, 43.8%)
		Worsened	7 (9.1%)	(3.7%, 17.8%)	10 (13.3%)	(6.6%, 23.2%)
Sense of smell/taste	Week 8	Improved	33 (42.3%)	(31.2%, 54.0%)	26 (34.7%)	(24.0%, 46.5%)
		No change	33 (42.3%)	(31.2%, 54.0%)	32 (42.7%)	(31.3%, 54.6%)
		Worsened	12 (15.4%)	(8.2%, 25.3%)	17 (22.7%)	(13.8%, 33.8%)
	Week 24	Improved	30 (39.0%)	(28.0%, 50.8%)	26 (34.7%)	(24.0%, 46.5%)
		No change	29 (37.7%)	(26.9%, 49.4%)	38 (50.7%)	(38.9%, 62.4%)
		Worsened	18 (23.4%)	(14.5%, 34.4%)	11 (14.7%)	(7.6%, 24.7%)
Cough	Week 8	Improved	21 (26.9%)	(17.5%, 38.2%)	27 (36.0%)	(25.2%, 47.9%)
		No change	47 (60.3%)	(48.5%, 71.2%)	36 (48.0%)	(36.3%, 59.8%)
		Worsened	10 (12.8%)	(6.3%, 22.3%)	12 (16.0%)	(8.6%, 26.3%)
	Week 24	Improved	18 (23.4%)	(14.5%, 34.4%)	25 (33.3%)	(22.9%, 45.2%)
		No change	42 (54.5%)	(42.8%, 65.9%)	39 (52.0%)	(40.2%, 63.7%)
		Worsened	17 (22.1%)	(13.4%, 33.0%)	11 (14.7%)	(7.6%, 24.7%)
Post-nasal discharge	Week 8	Improved	33 (42.3%)	(31.2%, 54.0%)	23 (30.7%)	(20.5%, 42.4%)
		No change	23 (29.5%)	(19.7%, 40.9%)	31 (41.3%)	(30.1%, 53.3%)
		Worsened	22 (28.2%)	(18.6%, 39.5%)	21 (28.0%)	(18.2%, 39.6%)
	Week 24	Improved	33 (42.9%)	(31.6%, 54.6%)	34 (45.3%)	(33.8%, 57.3%)
		No change	20 (26.0%)	(16.6%, 37.2%)	22 (29.3%)	(19.4%, 41.0%)
		Worsened	24 (31.2%)	(21.1%, 42.7%)	19 (25.3%)	(16.0%, 36.7%)
Thick nasal discharge	Week 8	Improved	37 (47.4%)	(36.0%, 59.1%)	24 (32.0%)	(21.7%, 43.8%)
		No change	29 (37.2%)	(26.5%, 48.9%)	35 (46.7%)	(35.1%, 58.6%)
		Worsened	12 (15.4%)	(8.2%, 25.3%)	16 (21.3%)	(12.7%, 32.3%)

Parameter	Visit	Change from baseline	Active + Active N=81		Placebo + Active N=79	
			n (%)	95% CI*	n (%)	95% CI*
	Week 24	Improved	33 (42.9%)	(31.6%, 54.6%)	23 (30.7%)	(20.5%, 42.4%)
		No change	29 (37.7%)	(26.9%, 49.4%)	36 (48.0%)	(36.3%, 59.8%)
		Worsened	15 (19.5%)	(11.3%, 30.1%)	16 (21.3%)	(12.7%, 32.3%)
Ear fullnes	Week 8	Improved	37 (47.4%)	(36.0%, 59.1%)	30 (40.0%)	(28.9%, 52.0%)
		No change	31 (39.7%)	(28.8%, 51.5%)	34 (45.3%)	(33.8%, 57.3%)
		Worsened	10 (12.8%)	(6.3%, 22.3%)	11 (14.7%)	(7.6%, 24.7%)
	Week 24	Improved	35 (45.5%)	(34.1%, 57.2%)	32 (42.7%)	(31.3%, 54.6%)
		No change	29 (37.7%)	(26.9%, 49.4%)	32 (42.7%)	(31.3%, 54.6%)
		Worsened	13 (16.9%)	(9.3%, 27.1%)	11 (14.7%)	(7.6%, 24.7%)
Dizziness	Week 8	Improved	22 (28.2%)	(18.6%, 39.5%)	15 (20.0%)	(11.6%, 30.8%)
		No change	49 (62.8%)	(51.1%, 73.5%)	42 (56.0%)	(44.1%, 67.5%)
		Worsened	7 (9.0%)	(3.7%, 17.6%)	18 (24.0%)	(14.9%, 35.3%)
	Week 24	Improved	20 (26.0%)	(16.6%, 37.2%)	16 (21.3%)	(12.7%, 32.3%)
		No change	45 (58.4%)	(46.6%, 69.6%)	47 (62.7%)	(50.7%, 73.6%)
		Worsened	12 (15.6%)	(8.3%, 25.6%)	12 (16.0%)	(8.6%, 26.3%)
Ear pain	Week 8	Improved	14 (17.9%)	(10.2%, 28.3%)	13 (17.3%)	(9.6%, 27.8%)
		No change	58 (74.4%)	(63.2%, 83.6%)	58 (77.3%)	(66.2%, 86.2%)
		Worsened	6 (7.7%)	(2.9%, 16.0%)	4 (5.3%)	(1.5%, 13.1%)
	Week 24	Improved	15 (19.5%)	(11.3%, 30.1%)	14 (18.7%)	(10.6%, 29.3%)
		No change	52 (67.5%)	(55.9%, 77.8%)	51 (68.0%)	(56.2%, 78.3%)
		Worsened	10 (13.0%)	(6.4%, 22.6%)	10 (13.3%)	(6.6%, 23.2%)
Facial pain/pressure	Week 8	Improved	19 (24.4%)	(15.3%, 35.4%)	17 (22.7%)	(13.8%, 33.8%)
		No change	53 (67.9%)	(56.4%, 78.1%)	45 (60.0%)	(48.0%, 71.1%)
		Worsened	6 (7.7%)	(2.9%, 16.0%)	13 (17.3%)	(9.6%, 27.8%)
	Week 24	Improved	21 (27.3%)	(17.7%, 38.6%)	19 (25.3%)	(16.0%, 36.7%)
		No change	47 (61.0%)	(49.2%, 72.0%)	48 (64.0%)	(52.1%, 74.8%)
		Worsened	9 (11.7%)	(5.5%, 21.0%)	8 (10.7%)	(4.7%, 19.9%)
Difficulty falling asleep	Week 8	Improved	30 (38.5%)	(27.7%, 50.2%)	28 (37.3%)	(26.4%, 49.3%)
		No change	37 (47.4%)	(36.0%, 59.1%)	27 (36.0%)	(25.2%, 47.9%)
		Worsened	11 (14.1%)	(7.3%, 23.8%)	20 (26.7%)	(17.1%, 38.1%)
	Week 24	Improved	33 (42.9%)	(31.6%, 54.6%)	28 (37.3%)	(26.4%, 49.3%)
		No change	28 (36.4%)	(25.7%, 48.1%)	34 (45.3%)	(33.8%, 57.3%)
		Worsened	16 (20.8%)	(12.4%, 31.5%)	13 (17.3%)	(9.6%, 27.8%)
Waking up at night	Week 8	Improved	39 (50.0%)	(38.5%, 61.5%)	33 (44.0%)	(32.5%, 55.9%)
		No change	26 (33.3%)	(23.1%, 44.9%)	24 (32.0%)	(21.7%, 43.8%)
		Worsened	13 (16.7%)	(9.2%, 26.8%)	18 (24.0%)	(14.9%, 35.3%)
	Week 24	Improved	37 (48.1%)	(36.5%, 59.7%)	39 (52.0%)	(40.2%, 63.7%)
		No change	24 (31.2%)	(21.1%, 42.7%)	16 (21.3%)	(12.7%, 32.3%)
		Worsened	16 (20.8%)	(12.4%, 31.5%)	20 (26.7%)	(17.1%, 38.1%)
Lack of good night's sleep	Week 8	Improved	38 (48.7%)	(37.2%, 60.3%)	37 (49.3%)	(37.6%, 61.1%)
		No change	28 (35.9%)	(25.3%, 47.6%)	23 (30.7%)	(20.5%, 42.4%)
		Worsened	12 (15.4%)	(8.2%, 25.3%)	15 (20.0%)	(11.6%, 30.8%)
	Week 24	Improved	36 (46.8%)	(35.3%, 58.5%)	43 (57.3%)	(45.4%, 68.7%)
		No change	27 (35.1%)	(24.5%, 46.8%)	20 (26.7%)	(17.1%, 38.1%)
		Worsened	14 (18.2%)	(10.3%, 28.6%)	12 (16.0%)	(8.6%, 26.3%)

Parameter	Visit	Change from baseline	Active + Active N=81		Placebo + Active N=79	
			n (%)	95% CI*	n (%)	95% CI*
Waking up tired	Week 8	Improved	36 (46.2%)	(34.8%, 57.8%)	36 (48.0%)	(36.3%, 59.8%)
		No change	31 (39.7%)	(28.8%, 51.5%)	20 (26.7%)	(17.1%, 38.1%)
		Worsened	11 (14.1%)	(7.3%, 23.8%)	19 (25.3%)	(16.0%, 36.7%)
	Week 24	Improved	41 (53.2%)	(41.5%, 64.7%)	43 (57.3%)	(45.4%, 68.7%)
		No change	23 (29.9%)	(20.0%, 41.4%)	17 (22.7%)	(13.8%, 33.8%)
		Worsened	13 (16.9%)	(9.3%, 27.1%)	15 (20.0%)	(11.6%, 30.8%)
Fatigue	Week 8	Improved	38 (48.7%)	(37.2%, 60.3%)	30 (40.0%)	(28.9%, 52.0%)
		No change	27 (34.6%)	(24.2%, 46.2%)	31 (41.3%)	(30.1%, 53.3%)
		Worsened	13 (16.7%)	(9.2%, 26.8%)	14 (18.7%)	(10.6%, 29.3%)
	Week 24	Improved	33 (42.9%)	(31.6%, 54.6%)	38 (50.7%)	(38.9%, 62.4%)
		No change	28 (36.4%)	(25.7%, 48.1%)	22 (29.3%)	(19.4%, 41.0%)
		Worsened	16 (20.8%)	(12.4%, 31.5%)	15 (20.0%)	(11.6%, 30.8%)
Reduced productivity	Week 8	Improved	31 (39.7%)	(28.8%, 51.5%)	28 (37.3%)	(26.4%, 49.3%)
		No change	34 (43.6%)	(32.4%, 55.3%)	33 (44.0%)	(32.5%, 55.9%)
		Worsened	13 (16.7%)	(9.2%, 26.8%)	14 (18.7%)	(10.6%, 29.3%)
	Week 24	Improved	31 (40.3%)	(29.2%, 52.1%)	32 (42.7%)	(31.3%, 54.6%)
		No change	26 (33.8%)	(23.4%, 45.4%)	29 (38.7%)	(27.6%, 50.6%)
		Worsened	20 (26.0%)	(16.6%, 37.2%)	14 (18.7%)	(10.6%, 29.3%)
Reduced concentration	Week 8	Improved	32 (41.0%)	(30.0%, 52.7%)	25 (33.3%)	(22.9%, 45.2%)
		No change	38 (48.7%)	(37.2%, 60.3%)	36 (48.0%)	(36.3%, 59.8%)
		Worsened	8 (10.3%)	(4.5%, 19.2%)	14 (18.7%)	(10.6%, 29.3%)
	Week 24	Improved	26 (33.8%)	(23.4%, 45.4%)	28 (37.3%)	(26.4%, 49.3%)
		No change	36 (46.8%)	(35.3%, 58.5%)	32 (42.7%)	(31.3%, 54.6%)
		Worsened	15 (19.5%)	(11.3%, 30.1%)	15 (20.0%)	(11.6%, 30.8%)
Frustrated/restless/irritable	Week 8	Improved	35 (44.9%)	(33.6%, 56.6%)	20 (26.7%)	(17.1%, 38.1%)
		No change	33 (42.3%)	(31.2%, 54.0%)	32 (42.7%)	(31.3%, 54.6%)
		Worsened	10 (12.8%)	(6.3%, 22.3%)	23 (30.7%)	(20.5%, 42.4%)
	Week 24	Improved	32 (41.6%)	(30.4%, 53.4%)	26 (34.7%)	(24.0%, 46.5%)
		No change	31 (40.3%)	(29.2%, 52.1%)	35 (46.7%)	(35.1%, 58.6%)
		Worsened	14 (18.2%)	(10.3%, 28.6%)	14 (18.7%)	(10.6%, 29.3%)
Sad	Week 8	Improved	21 (26.9%)	(17.5%, 38.2%)	18 (24.0%)	(14.9%, 35.3%)
		No change	48 (61.5%)	(49.8%, 72.3%)	42 (56.0%)	(44.1%, 67.5%)
		Worsened	9 (11.5%)	(5.4%, 20.8%)	15 (20.0%)	(11.6%, 30.8%)
	Week 24	Improved	17 (22.1%)	(13.4%, 33.0%)	18 (24.0%)	(14.9%, 35.3%)
		No change	52 (67.5%)	(55.9%, 77.8%)	48 (64.0%)	(52.1%, 74.8%)
		Worsened	8 (10.4%)	(4.6%, 19.4%)	9 (12.0%)	(5.6%, 21.6%)
Embarrassed	Week 8	Improved	41 (52.6%)	(40.9%, 64.0%)	34 (45.3%)	(33.8%, 57.3%)
		No change	28 (35.9%)	(25.3%, 47.6%)	26 (34.7%)	(24.0%, 46.5%)
		Worsened	9 (11.5%)	(5.4%, 20.8%)	15 (20.0%)	(11.6%, 30.8%)
	Week 24	Improved	32 (41.6%)	(30.4%, 53.4%)	37 (49.3%)	(37.6%, 61.1%)
		No change	34 (44.2%)	(32.8%, 55.9%)	22 (29.3%)	(19.4%, 41.0%)
		Worsened	11 (14.3%)	(7.4%, 24.1%)	16 (21.3%)	(12.7%, 32.3%)

*Confidence intervals calculated using Clopper-Pearson method

Table 14.43 SNOT-22 item reported as one of the five most significant problems Weeks 8 and 24, FAS

		Active + Active N=81		Placebo + Active N=79	
Parameter	**Week**	**n (%)**	**95% CI***	**n (%)**	**95% CI***
Need to blow nose	Week 8	27 (34.6%)	(24.2%, 46.2%)	31 (41.3%)	(30.1%, 53.3%)
	Week 24	29 (37.7%)	(26.9%, 49.4%)	25 (33.3%)	(22.9%, 45.2%)
Sneezing	Week 8	12 (15.4%)	(8.2%, 25.3%)	10 (13.3%)	(6.6%, 23.2%)
	Week 24	13 (16.9%)	(9.3%, 27.1%)	9 (12.0%)	(5.6%, 21.6%)
Runny nose	Week 8	20 (25.6%)	(16.4%, 36.8%)	25 (33.3%)	(22.9%, 45.2%)
	Week 24	24 (31.2%)	(21.1%, 42.7%)	21 (28.0%)	(18.2%, 39.6%)
Blockage/congestion of nose	Week 8	63 (80.8%)	(70.3%, 88.8%)	65 (86.7%)	(76.8%, 93.4%)
	Week 24	68 (88.3%)	(79.0%, 94.5%)	64 (85.3%)	(75.3%, 92.4%)
Sense of smell/taste	Week 8	9 (11.5%)	(5.4%, 20.8%)	4 (5.3%)	(1.5%, 13.1%)
	Week 24	14 (18.2%)	(10.3%, 28.6%)	10 (13.3%)	(6.6%, 23.2%)
Cough	Week 8	4 (5.1%)	(1.4%, 12.6%)	6 (8.0%)	(3.0%, 16.6%)
	Week 24	6 (7.8%)	(2.9%, 16.2%)	2 (2.7%)	(0.3%, 9.3%)
Post-nasal discharge	Week 8	26 (33.3%)	(23.1%, 44.9%)	26 (34.7%)	(24.0%, 46.5%)
	Week 24	27 (35.1%)	(24.5%, 46.8%)	20 (26.7%)	(17.1%, 38.1%)
Thick nasal discharge	Week 8	5 (6.4%)	(2.1%, 14.3%)	6 (8.0%)	(3.0%, 16.6%)
	Week 24	8 (10.4%)	(4.6%, 19.4%)	7 (9.3%)	(3.8%, 18.3%)
Ear fullnes	Week 8	10 (12.8%)	(6.3%, 22.3%)	6 (8.0%)	(3.0%, 16.6%)
	Week 24	11 (14.3%)	(7.4%, 24.1%)	9 (12.0%)	(5.6%, 21.6%)
Dizziness	Week 8	2 (2.6%)	(0.3%, 9.0%)	3 (4.0%)	(0.8%, 11.2%)
	Week 24	2 (2.6%)	(0.3%, 9.1%)	2 (2.7%)	(0.3%, 9.3%)
Ear pain	Week 8	3 (3.8%)	(0.8%, 10.8%)	2 (2.7%)	(0.3%, 9.3%)
	Week 24	0	(0.0%, 4.7%)	3 (4.0%)	(0.8%, 11.2%)
Facial pain/pressure	Week 8	9 (11.5%)	(5.4%, 20.8%)	5 (6.7%)	(2.2%, 14.9%)
	Week 24	8 (10.4%)	(4.6%, 19.4%)	5 (6.7%)	(2.2%, 14.9%)
Difficulty falling asleep	Week 8	17 (21.8%)	(13.2%, 32.6%)	14 (18.7%)	(10.6%, 29.3%)
	Week 24	10 (13.0%)	(6.4%, 22.6%)	15 (20.0%)	(11.6%, 30.8%)
Waking up at night	Week 8	26 (33.3%)	(23.1%, 44.9%)	23 (30.7%)	(20.5%, 42.4%)
	Week 24	25 (32.5%)	(22.2%, 44.1%)	21 (28.0%)	(18.2%, 39.6%)
Lack of good night's sleep	Week 8	17 (21.8%)	(13.2%, 32.6%)	18 (24.0%)	(14.9%, 35.3%)
	Week 24	22 (28.6%)	(18.8%, 40.0%)	18 (24.0%)	(14.9%, 35.3%)
Waking up tired	Week 8	30 (38.5%)	(27.7%, 50.2%)	33 (44.0%)	(32.5%, 55.9%)
	Week 24	23 (29.9%)	(20.0%, 41.4%)	26 (34.7%)	(24.0%, 46.5%)
Fatigue	Week 8	20 (25.6%)	(16.4%, 36.8%)	21 (28.0%)	(18.2%, 39.6%)
	Week 24	13 (16.9%)	(9.3%, 27.1%)	19 (25.3%)	(16.0%, 36.7%)
Reduced productivity	Week 8	11 (14.1%)	(7.3%, 23.8%)	3 (4.0%)	(0.8%, 11.2%)
	Week 24	10 (13.0%)	(6.4%, 22.6%)	3 (4.0%)	(0.8%, 11.2%)
Reduced concentration	Week 8	8 (10.3%)	(4.5%, 19.2%)	3 (4.0%)	(0.8%, 11.2%)
	Week 24	7 (9.1%)	(3.7%, 17.8%)	5 (6.7%)	(2.2%, 14.9%)
Frustrated / restless/irritable	Week 8	5 (6.4%)	(2.1%, 14.3%)	6 (8.0%)	(3.0%, 16.6%)
	Week 24	6 (7.8%)	(2.9%, 16.2%)	8 (10.7%)	(4.7%, 19.9%)
Sad	Week 8	2 (2.6%)	(0.3%, 9.0%)	1 (1.3%)	(0.0%, 7.2%)
	Week 24	4 (5.2%)	(1.4%, 12.8%)	0	(0.0%, 4.8%)

Parameter	Week	Active + Active N=81 n (%)	Active + Active N=81 95% CI*	Placebo + Active N=79 n (%)	Placebo + Active N=79 95% CI*
Besvärad / generad pga dina näs-bihålebesvär *(Embarrassed)*	Week 8	16 (20.5%)	(12.2%, 31.2%)	20 (26.7%)	(17.1%, 38.1%)
	Week 24	22 (28.6%)	(18.8%, 40.0%)	16 (21.3%)	(12.7%, 32.3%)

*Confidence intervals calculated using Clopper-Pearson method

Table 14.44 EQ-5D-3L up to Week 4, FAS

Parameter	Week	Score	Active N=81 n (%)	Active N=81 95% CI*	Placebo N=79 n (%)	Placebo N=79 95% CI*
Mobility	Week -1 Screening	No problems	77 (95.1%)	(87.8%, 98.6%)	76 (96.2%)	(89.3%, 99.2%)
		Some or moderate problems	4 (4.9%)	(1.4%, 12.2%)	3 (3.8%)	(0.8%, 10.7%)
		Extreme problems	0	(0.0%, 4.5%)	0	(0.0%, 4.6%)
	Week 0	No problems	74 (91.4%)	(83.0%, 96.5%)	77 (97.5%)	(91.2%, 99.7%)
		Some or moderate problems	7 (8.6%)	(3.5%, 17.0%)	2 (2.5%)	(0.3%, 8.8%)
		Extreme problems	0	(0.0%, 4.5%)	0	(0.0%, 4.6%)
	Week 4	No problems	76 (95.0%)	(87.7%, 98.6%)	74 (96.1%)	(89.0%, 99.2%)
		Some or moderate problems	4 (5.0%)	(1.4%, 12.3%)	3 (3.9%)	(0.8%, 11.0%)
		Extreme problems	0	(0.0%, 4.5%)	0	(0.0%, 4.7%)
Self-Care	Week -1 Screening	No problems	81 (100.0%)	(95.5%, 100.0%)	78 (98.7%)	(93.1%, 100.0%)
		Some or moderate problems	0	(0.0%, 4.5%)	1 (1.3%)	(0.0%, 6.9%)
		Extreme problems	0	(0.0%, 4.5%)	0	(0.0%, 4.6%)
	Week 0	No problems	81 (100.0%)	(95.5%, 100.0%)	78 (98.7%)	(93.1%, 100.0%)
		Some or moderate problems	0	(0.0%, 4.5%)	0	(0.0%, 4.6%)
		Extreme problems	0	(0.0%, 4.5%)	1 (1.3%)	(0.0%, 6.9%)
	Week 4	No problems	80 (100.0%)	(95.5%, 100.0%)	76 (98.7%)	(93.0%, 100.0%)
		Some or moderate problems	0	(0.0%, 4.5%)	1 (1.3%)	(0.0%, 7.0%)
		Extreme problems	0	(0.0%, 4.5%)	0	(0.0%, 4.7%)
Usual Activities	Week -1 Screening	No problems	78 (96.3%)	(89.6%, 99.2%)	75 (94.9%)	(87.5%, 98.6%)
		Some or moderate problems	3 (3.7%)	(0.8%, 10.4%)	4 (5.1%)	(1.4%, 12.5%)
		Extreme problems	0	(0.0%, 4.5%)	0	(0.0%, 4.6%)
	Week 0	No problems	77 (95.1%)	(87.8%, 98.6%)	77 (97.5%)	(91.2%, 99.7%)
		Some or moderate problems	4 (4.9%)	(1.4%, 12.2%)	1 (1.3%)	(0.0%, 6.9%)
		Extreme problems	0	(0.0%, 4.5%)	1 (1.3%)	(0.0%, 6.9%)
	Week 4	No problems	76 (95.0%)	(87.7%, 98.6%)	74 (96.1%)	(89.0%, 99.2%)
		Some or moderate problems	4 (5.0%)	(1.4%, 12.3%)	2 (2.6%)	(0.3%, 9.1%)
		Extreme problems	0	(0.0%, 4.5%)	1 (1.3%)	(0.0%, 7.0%)
Pain/ Discomfort	Week -1 Screening	No problems	51 (63.0%)	(51.5%, 73.4%)	42 (53.2%)	(41.6%, 64.5%)
		Some or moderate problems	27 (33.3%)	(23.2%, 44.7%)	36 (45.6%)	(34.3%, 57.2%)
		Extreme problems	3 (3.7%)	(0.8%, 10.4%)	1 (1.3%)	(0.0%, 6.9%)
	Week 0	No problems	49 (60.5%)	(49.0%, 71.2%)	47 (59.5%)	(47.9%, 70.4%)
		Some or moderate problems	29 (35.8%)	(25.4%, 47.2%)	31 (39.2%)	(28.4%, 50.9%)
		Extreme problems	3 (3.7%)	(0.8%, 10.4%)	1 (1.3%)	(0.0%, 6.9%)
	Week 4	No problems	49 (61.3%)	(49.7%, 71.9%)	35 (45.5%)	(34.1%, 57.2%)
		Some or moderate problems	27 (33.8%)	(23.6%, 45.2%)	39 (50.6%)	(39.0%, 62.2%)
		Extreme problems	4 (5.0%)	(1.4%, 12.3%)	3 (3.9%)	(0.8%, 11.0%)

Parameter	Week	Score	Active N=81 n (%)	Active N=81 95% CI*	Placebo N=79 n (%)	Placebo N=79 95% CI*
Anxiety/ Depression	Week -1 Screening	No problems	63 (77.8%)	(67.2%, 86.3%)	65 (82.3%)	(72.1%, 90.0%)
		Some or moderate problems	18 (22.2%)	(13.7%, 32.8%)	13 (16.5%)	(9.1%, 26.5%)
		Extreme problems	0	(0.0%, 4.5%)	1 (1.3%)	(0.0%, 6.9%)
	Week 0	No problems	70 (86.4%)	(77.0%, 93.0%)	68 (86.1%)	(76.5%, 92.8%)
		Some or moderate problems	10 (12.3%)	(6.1%, 21.5%)	10 (12.7%)	(6.2%, 22.0%)
		Extreme problems	1 (1.2%)	(0.0%, 6.7%)	1 (1.3%)	(0.0%, 6.9%)
	Week 4	No problems	67 (83.8%)	(73.8%, 91.1%)	59 (76.6%)	(65.6%, 85.5%)
		Some or moderate problems	13 (16.3%)	(8.9%, 26.2%)	18 (23.4%)	(14.5%, 34.4%)
		Extreme problems	0	(0.0%, 4.5%)	0	(0.0%, 4.7%)

* Confidence intervals calculated using Clopper-Pearson method

Table 14.45 Summary of EQ-5D-3L VAS up to Week 4, FAS

Week	Statistic	Active N=81	Placebo N=79
Screening	n	81	79
	Mean (SD)	77.65 (13.91)	81.24 (14.25)
	95% CI	(74.58, 80.73)	(78.05, 84.43)
	Median	80.00	82.00
	Q1, Q3	70.00, 90.00	73.00, 94.00
	Min, Max	5.0, 98.0	40.0, 100.0
Week 0	n	81	79
	Mean (SD)	77.58 (14.80)	82.39 (14.15)
	95% CI	(74.31, 80.85)	(79.22, 85.56)
	Median	80.00	86.00
	Q1, Q3	70.00, 89.00	71.00, 95.00
	Min, Max	2.0, 100.0	37.0, 100.0
Change from baseline, Week 0	n	81	79
	Mean (SD)	-0.07 (8.87)	1.15 (8.03)
	95% CI	(-2.04, 1.89)	(-0.65, 2.95)
	Median	0.00	0.00
	Q1, Q3	-2.00, 5.00	-1.00, 4.00
	Min, Max	-40.0, 19.0	-25.0, 21.0
Week 4	n	80	77
	Mean (SD)	78.15 (15.82)	80.04 (12.74)
	95% CI	(74.63, 81.67)	(77.15, 82.93)
	Median	80.00	81.00
	Q1, Q3	70.00, 90.00	70.00, 90.00
	Min, Max	5.0, 100.0	50.0, 100.0
Change from baseline, Week 4	n	80	77
	Mean (SD)	0.68 (10.54)	-1.10 (9.08)
	95% CI	(-1.67, 3.02)	(-3.16, 0.96)
	Median	0.00	0.00
	Q1, Q3	-2.50, 5.50	-8.00, 3.00
	Min, Max	-39.0, 26.0	-20.0, 28.0

Table 14.46 EQ-5D-3L up to Weeks 8 and 24, FAS

			Active + Active N=81		Placebo + Active N=79	
Parameter	**Visit**	**Score**	**n (%)**	**95% CI***	**n (%)**	**95% C*I**
Mobility	Week 8	No problems	76 (97.4%)	(91.0%, 99.7%)	73 (97.3%)	(90.7%, 99.7%)
		Some or moderate problems	2 (2.6%)	(0.3%, 9.0%)	2 (2.7%)	(0.3%, 9.3%)
		Extreme problems	0	(0.0%, 4.6%)	0	(0.0%, 4.8%)
	Week 24	No problems	72 (93.5%)	(85.5%, 97.9%)	71 (94.7%)	(86.9%, 98.5%)
		Some or moderate problems	5 (6.5%)	(2.1%, 14.5%)	4 (5.3%)	(1.5%, 13.1%)
		Extreme problems	0	(0.0%, 4.7%)	0	(0.0%, 4.8%)
Self-Care	Week 8	No problems	78 (100.0%)	(95.4%, 100.0%)	74 (98.7%)	(92.8%, 100.0%)
		Some or moderate problems	0	(0.0%, 4.6%)	1 (1.3%)	(0.0%, 7.2%)
		Extreme problems	0	(0.0%, 4.6%)	0	(0.0%, 4.8%)
	Week 24	No problems	77 (100.0%)	(95.3%, 100.0%)	75 (100.0%)	(95.2%, 100.0%)
		Some or moderate problems	0	(0.0%, 4.7%)	0	(0.0%, 4.8%)
		Extreme problems	0	(0.0%, 4.7%)	0	(0.0%, 4.8%)
Usual Activities	Week 8	No problems	75 (96.2%)	(89.2%, 99.2%)	72 (96.0%)	(88.8%, 99.2%)
		Some or moderate problems	3 (3.8%)	(0.8%, 10.8%)	3 (4.0%)	(0.8%, 11.2%)
		Extreme problems	0	(0.0%, 4.6%)	0	(0.0%, 4.8%)
	Week 24	No problems	73 (94.8%)	(87.2%, 98.6%)	72 (96.0%)	(88.8%, 99.2%)
		Some or moderate problems	3 (3.9%)	(0.8%, 11.0%)	3 (4.0%)	(0.8%, 11.2%)
		Extreme problems	1 (1.3%)	(0.0%, 7.0%)	0	(0.0%, 4.8%)
Pain/Discomfort	Week 8	No problems	56 (71.8%)	(60.5%, 81.4%)	42 (56.0%)	(44.1%, 67.5%)
		Some or moderate problems	20 (25.6%)	(16.4%, 36.8%)	31 (41.3%)	(30.1%, 53.3%)
		Extreme problems	2 (2.6%)	(0.3%, 9.0%)	2 (2.7%)	(0.3%, 9.3%)
	Week 24	No problems	43 (55.8%)	(44.1%, 67.2%)	46 (61.3%)	(49.4%, 72.4%)
		Some or moderate problems	32 (41.6%)	(30.4%, 53.4%)	27 (36.0%)	(25.2%, 47.9%)
		Extreme problems	2 (2.6%)	(0.3%, 9.1%)	2 (2.7%)	(0.3%, 9.3%)
Anxiety/Depression	Week 8	No problems	62 (79.5%)	(68.8%, 87.8%)	58 (77.3%)	(66.2%, 86.2%)
		Some or moderate problems	15 (19.2%)	(11.2%, 29.7%)	16 (21.3%)	(12.7%, 32.3%)
		Extreme problems	1 (1.3%)	(0.0%, 6.9%)	1 (1.3%)	(0.0%, 7.2%)
	Week 24	No problems	58 (75.3%)	(64.2%, 84.4%)	55 (73.3%)	(61.9%, 82.9%)
		Some or moderate problems	18 (23.4%)	(14.5%, 34.4%)	20 (26.7%)	(17.1%, 38.1%)
		Extreme problems	1 (1.3%)	(0.0%, 7.0%)	0	(0.0%, 4.8%)

* Confidence intervals calculated using Clopper-Pearson method

Table 14.47 Summary of EQ VAS Week 8 and 24, FAS

Week	Statistic	Active + Active N=81	Placebo + Active N=79
Week 8	n	77	75
	Mean (SD)	81.38 (13.15)	81.68 (14.49)
	95% CI	(78.39, 84.36)	(78.35, 85.01)
	Median	82.00	84.00
	Q1, Q3	75.00, 90.00	72.00, 93.00
	Min, Max	16.0, 100.0	25.0, 100.0
Change from baseline, Week 8	n	77	75
	Mean (SD)	3.35 (8.73)	0.95 (10.17)
	95% CI	(1.37, 5.33)	(-1.39, 3.29)
	Median	3.00	0.00
	Q1, Q3	0.00, 8.00	-4.00, 5.00
	Min, Max	-20.0, 27.0	-35.0, 35.0
Week 24	n	77	75
	Mean (SD)	78.94 (15.47)	82.27 (14.67)
	95% CI	(75.42, 82.45)	(78.89, 85.64)
	Median	81.00	85.00
	Q1, Q3	72.00, 90.00	75.00, 95.00
	Min, Max	2.0, 100.0	35.0, 100.0
Change from baseline, Week 24	n	77	75
	Mean (SD)	1.36 (12.34)	1.53 (11.43)
	95% CI	(-1.44, 4.16)	(-1.10, 4.16)
	Median	2.00	1.00
	Q1, Q3	-5.00, 10.00	-3.00, 8.00
	Min, Max	-30.0, 31.0	-31.0, 45.0

14.4 SAFETY DATA

14.4.1 Displays of Adverse Events

Table 14.48 Overview of AEs, Safety analysis set

	Active + Active N=81		Low amplitude control + Active N=47		Placebo + Active N=79		Total N=207	
Event	**n (%)**	**Events**	**n (%)**	**Events**	**n (%)**	**Events**	**n (%)**	**Events**
AEs	44 (54.3%)	77	17 (36.2%)	23	59 (74.7%)	126	120 (58.0%)	226
SAEs	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
ADE[1]	7 (8.6%)	7	3 (6.4%)	3	10 (12.7%)	11	20 (9.7%)	21
SADEs[1]	0	0	0	0	0	0	0	0
Causality (relationship to investigational device)[2]								
Not related	43 (97.7%)	74	16 (94.1%)	21	56 (94.9%)	120	115 (95.8%)	215
Related to device[3]	3 (6.8%)	3	2 (11.8%)	2	6 (10.2%)	6	11 (9.2%)	11
Severity[2]								
Mild	34 (77.3%)	55	9 (52.9%)	11	33 (55.9%)	84	76 (63.3%)	150
Moderate	17 (38.6%)	22	8 (47.1%)	10	31 (52.5%)	39	56 (46.7%)	71
Severe	0	0	2 (11.8%)	2	3 (5.1%)	3	5 (4.2%)	5

n = number of patients

Percentages are based on the number of subjects within each treatment group

AEs with partially missing start date were calculated as starting before second treatment

[1] Events related to the investigational procedure

[2] Percentages are based on the total number of AEs within each treatment group.

[3] Procedure related events which are also assessed as being device-related

Table 14.49 AEs by SOC and PT during the entire study period, Safety analysis set

System Organ Class/Preferred Term*	Active + Active N=81		Low amplitude control + Active N=47		Placebo + Active N=79		Total N=207	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Any adverse event	44 (54.3%)	77	17 (36.2%)	23	59 (74.7%)	126	120 (58.0%)	226
Infections and infestations	**28 (34.6%)**	**37**	**10 (21.3%)**	**11**	**41 (51.9%)**	**52**	**79 (38.2%)**	**100**
Nasopharyngitis	25 (30.9%)	30	6 (12.8%)	7	35 (44.3%)	44	66 (31.9%)	81
Sinusitis	1 (1.2%)	1	2 (4.3%)	2	1 (1.3%)	1	4 (1.9%)	4
Urinary tract infection	2 (2.5%)	3	0	0	0	0	2 (1.0%)	3
Gastroenteritis	0	0	1 (2.1%)	1	1 (1.3%)	1	2 (1.0%)	2
Upper respiratory tract infection	1 (1.2%)	1	0	0	1 (1.3%)	1	2 (1.0%)	2
Gastroenteritis viral	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Tonsillitis	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Borrelia infection	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Enterobiasis	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Influenza	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Laryngitis	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Vaginal infection	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Vaginitis bacterial	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Respiratory, thoracic and mediastinal disorders	**6 (7.4%)**	**7**	**4 (8.5%)**	**5**	**16 (20.3%)**	**20**	**26 (12.6%)**	**32**
Sneezing	2 (2.5%)	2	1 (2.1%)	1	4 (5.1%)	4	7 (3.4%)	7
Cough	2 (2.5%)	2	1 (2.1%)	1	3 (3.8%)	4	6 (2.9%)	7
Rhinorrhoea	0	0	0	0	3 (3.8%)	3	3 (1.4%)	3
Dyspnoea	0	0	1 (2.1%)	2	1 (1.3%)	1	2 (1.0%)	3
Increased upper airway secretion	0	0	0	0	2 (2.5%)	2	2 (1.0%)	2
Oropharyngeal pain	1 (1.2%)	1	0	0	1 (1.3%)	1	2 (1.0%)	2
Rhinalgia	1 (1.2%)	1	0	0	1 (1.3%)	1	2 (1.0%)	2
Dysphonia	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Nasal polyps	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1

System Organ Class/Preferred Term*	Active + Active N=81		Low amplitude control + Active N=47		Placebo + Active N=79		Total N=207	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Epistaxis	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Nasal discomfort	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Nasal dryness	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Nasal ulcer	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Nervous system disorders	**9 (11.1%)**	**17**	**2 (4.3%)**	**2**	**14 (17.7%)**	**29**	**25 (12.1%)**	**48**
Headache	5 (6.2%)	9	0	0	10 (12.7%)	25	15 (7.2%)	34
Migraine	4 (4.9%)	6	0	0	0	0	4 (1.9%)	6
Dizziness	0	0	0	0	2 (2.5%)	2	2 (1.0%)	2
Anosmia	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Cervicobrachial syndrome	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Cerebrovascular accident	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Epilepsy	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Balance disorder	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Carpal tunnel syndrome	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Musculoskeletal and connective tissue disorders	**2 (2.5%)**	**2**	**1 (2.1%)**	**1**	**6 (7.6%)**	**7**	**9 (4.3%)**	**10**
Musculoskeletal pain	0	0	0	0	2 (2.5%)	2	2 (1.0%)	2
Arthralgia	0	0	1 (2.1%)	1	1 (1.3%)	1	2 (1.0%)	2
Costochondritis	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Jaw disorder	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Fibromyalgia	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Myalgia	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Periarthritis	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Temporomandibular joint syndrome	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Injury, poisoning and procedural complications	**3 (3.7%)**	**3**	**1 (2.1%)**	**1**	**4 (5.1%)**	**4**	**8 (3.9%)**	**8**
Ligament sprain	2 (2.5%)	2	0	0	1 (1.3%)	1	3 (1.4%)	3
Fall	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1

System Organ Class/Preferred Term*	Active + Active N=81		Low amplitude control + Active N=47		Placebo + Active N=79		Total N=207	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Chest injury	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Joint dislocation	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Post-traumatic neck syndrome	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Wrist fracture	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
General disorders and administration site conditions	**2 (2.5%)**	**2**	**1 (2.1%)**	**1**	**4 (5.1%)**	**4**	**7 (3.4%)**	**7**
Inflammation	1 (1.2%)	1	0	0	2 (2.5%)	2	3 (1.4%)	3
Pain	0	0	1 (2.1%)	1	1 (1.3%)	1	2 (1.0%)	2
Pyrexia	1 (1.2%)	1	0	0	1 (1.3%)	1	2 (1.0%)	2
Gastrointestinal disorders	**1 (1.2%)**	**3**	**1 (2.1%)**	**1**	**3 (3.8%)**	**5**	**5 (2.4%)**	**9**
Gastritis	0	0	0	0	1 (1.3%)	3	1 (0.5%)	3
Diarrhoea	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Gastrointestinal pain	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Melaena	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Toothache	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Nausea	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Vomiting	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Surgical and medical procedures	**1 (1.2%)**	**1**	**1 (2.1%)**	**1**	**2 (2.5%)**	**2**	**4 (1.9%)**	**4**
Benign breast lump removal	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Intraocular lens implant	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Cataract operation	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Tooth extraction	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Ear and labyrinth disorders	**2 (2.5%)**	**2**	**0**	**0**	**0**	**0**	**2 (1.0%)**	**2**
Ear pain	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Eustachian tube dysfunction	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Reproductive system and breast disorders	**0**	**0**	**0**	**0**	**2 (2.5%)**	**2**	**2 (1.0%)**	**2**
Ovarian cyst	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1

System Organ Class/Preferred Term*	Active + Active N=81		Low amplitude control + Active N=47		Placebo + Active N=79		Total N=207	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Prostatitis	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Endocrine disorders	**1 (1.2%)**	**1**	**0**	**0**	**0**	**0**	**1 (0.5%)**	**1**
Hypothyroidism	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.2%)**	**1**	**0**	**0**	**0**	**0**	**1 (0.5%)**	**1**
Prolactinoma	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Skin and subcutaneous tissue disorders	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Swelling face	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Metabolism and nutrition disorders	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Gout	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1

n = number of subjects, Percentages are based on the number of subjects within each treatment group, *Coded acc to MedDRA version 16.0E
Adverse events with partially missing start date were calculated as starting before second treatment

Table 14.50 AEs by SOC and PT up to second treatment (Week 4), Safety analysis set

System Organ Class/Preferred Term*	Active N=81		Low amplitude control N=47		Placebo N=79		Total N=207	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Any adverse event	22 (27.2%)	30	8 (17.0%)	10	31 (39.2%)	45	61 (29.5%)	85
Infections and infestations	**10 (12.3%)**	**10**	**4 (8.5%)**	**4**	**14 (17.7%)**	**15**	**28 (13.5%)**	**29**
Nasopharyngitis	7 (8.6%)	7	3 (6.4%)	3	13 (16.5%)	14	23 (11.1%)	24
Gastroenteritis viral	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Tonsillitis	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Urinary tract infection	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Gastroenteritis	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Vaginitis bacterial	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Nervous system disorders	**7 (8.6%)**	**12**	**1 (2.1%)**	**1**	**6 (7.6%)**	**10**	**14 (6.8%)**	**23**
Headache	4 (4.9%)	8	0	0	4 (5.1%)	8	8 (3.9%)	16
Migraine	3 (3.7%)	4	0	0	0	0	3 (1.4%)	4
Cerebrovascular accident	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Balance disorder	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Carpal tunnel syndrome	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Respiratory, thoracic and mediastinal disorders	**3 (3.7%)**	**3**	**1 (2.1%)**	**1**	**6 (7.6%)**	**6**	**10 (4.8%)**	**10**
Increased upper airway secretion	0	0	0	0	2 (2.5%)	2	2 (1.0%)	2
Cough	1 (1.2%)	1	0	0	1 (1.3%)	1	2 (1.0%)	2
Sneezing	1 (1.2%)	1	0	0	1 (1.3%)	1	2 (1.0%)	2
Dysphonia	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Dyspnoea	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Epistaxis	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Rhinorrhoea	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Musculoskeletal and connective tissue disorders	**1 (1.2%)**	**1**	**1 (2.1%)**	**1**	**5 (6.3%)**	**6**	**7 (3.4%)**	**8**
Musculoskeletal pain	0	0	0	0	2 (2.5%)	2	2 (1.0%)	2
Arthralgia	0	0	1 (2.1%)	1	1 (1.3%)	1	2 (1.0%)	2

System Organ Class/Preferred Term*	Active N=81		Low amplitude control N=47		Placebo N=79		Total N=207	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Costochondritis	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Fibromyalgia	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Myalgia	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Temporomandibular joint syndrome	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
General disorders and administration site conditions	**1 (1.2%)**	**1**	**1 (2.1%)**	**1**	**3 (3.8%)**	**3**	**5 (2.4%)**	**5**
Inflammation	0	0	0	0	2 (2.5%)	2	2 (1.0%)	2
Pain	0	0	1 (2.1%)	1	1 (1.3%)	1	2 (1.0%)	2
Pyrexia	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Injury, poisoning and procedural complications	**2 (2.5%)**	**2**	**1 (2.1%)**	**1**	**1 (1.3%)**	**1**	**4 (1.9%)**	**4**
Ligament sprain	1 (1.2%)	1	0	0	1 (1.3%)	1	2 (1.0%)	2
Fall	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Chest injury	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Gastrointestinal disorders	**0**	**0**	**1 (2.1%)**	**1**	**1 (1.3%)**	**1**	**2 (1.0%)**	**2**
Toothache	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Gastritis	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Ear and labyrinth disorders	**1 (1.2%)**	**1**	**0**	**0**	**0**	**0**	**1 (0.5%)**	**1**
Ear pain	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Metabolism and nutrition disorders	**0**	**0**	**0**	**0**	**1 (1.3%)**	**1**	**1 (0.5%)**	**1**
Gout	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Reproductive system and breast disorders	**0**	**0**	**0**	**0**	**1 (1.3%)**	**1**	**1 (0.5%)**	**1**
Prostatitis	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Surgical and medical procedures	**0**	**0**	**0**	**0**	**1 (1.3%)**	**1**	**1 (0.5%)**	**1**
Tooth extraction	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1

n = number of subjects, Percentages are based on the number of subjects within each treatment group, *Coded acc to MedDRA version 16.0E

Adverse events with partially missing start date were calculated as starting before second treatment

Table 14.51 AEs by SOC and PT from second treatment (Week 4) to end of study, Safety analysis set

System Organ Class/Preferred Term*	Active + Active N=81		Low amplitude control + Active N=47		Placebo + Active N=79		Total N=207	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Any adverse event	34 (42.0%)	47	12 (25.5%)	13	45 (57.0%)	81	91 (44.0%)	141
Infections and infestations	**22 (27.2%)**	**27**	**7 (14.9%)**	**7**	**33 (41.8%)**	**37**	**62 (30.0%)**	**71**
Nasopharyngitis	19 (23.5%)	23	4 (8.5%)	4	27 (34.2%)	30	50 (24.2%)	57
Sinusitis	1 (1.2%)	1	2 (4.3%)	2	1 (1.3%)	1	4 (1.9%)	4
Urinary tract infection	2 (2.5%)	2	0	0	0	0	2 (1.0%)	2
Upper respiratory tract infection	1 (1.2%)	1	0	0	1 (1.3%)	1	2 (1.0%)	2
Borrelia infection	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Enterobiasis	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Gastroenteritis	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Influenza	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Laryngitis	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Vaginal infection	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Respiratory, thoracic and mediastinal disorders	**4 (4.9%)**	**4**	**4 (8.5%)**	**4**	**12 (15.2%)**	**14**	**20 (9.7%)**	**22**
Cough	1 (1.2%)	1	1 (2.1%)	1	3 (3.8%)	3	5 (2.4%)	5
Sneezing	1 (1.2%)	1	1 (2.1%)	1	3 (3.8%)	3	5 (2.4%)	5
Rhinorrhoea	0	0	0	0	2 (2.5%)	2	2 (1.0%)	2
Dyspnoea	0	0	1 (2.1%)	1	1 (1.3%)	1	2 (1.0%)	2
Oropharyngeal pain	1 (1.2%)	1	0	0	1 (1.3%)	1	2 (1.0%)	2
Rhinalgia	1 (1.2%)	1	0	0	1 (1.3%)	1	2 (1.0%)	2
Nasal polyps	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Nasal discomfort	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Nasal dryness	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Nasal ulcer	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Nervous system disorders	**4 (4.9%)**	**5**	**1 (2.1%)**	**1**	**10 (12.7%)**	**19**	**15 (7.2%)**	**25**
Headache	1 (1.2%)	1	0	0	8 (10.1%)	17	9 (4.3%)	18
Migraine	2 (2.5%)	2	0	0	0	0	2 (1.0%)	2

System Organ Class/Preferred Term*	Active + Active N=81		Low amplitude control + Active N=47		Placebo + Active N=79		Total N=207	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Dizziness	0	0	0	0	2 (2.5%)	2	2 (1.0%)	2
Anosmia	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Cervicobrachial syndrome	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Epilepsy	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Gastrointestinal disorders	**1 (1.2%)**	**3**	**0**	**0**	**3 (3.8%)**	**4**	**4 (1.9%)**	**7**
Gastritis	0	0	0	0	1 (1.3%)	2	1 (0.5%)	2
Diarrhoea	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Gastrointestinal pain	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Melaena	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Nausea	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Vomiting	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Injury, poisoning and procedural complications	**1 (1.2%)**	**1**	**0**	**0**	**3 (3.8%)**	**3**	**4 (1.9%)**	**4**
Ligament sprain	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Joint dislocation	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Post-traumatic neck syndrome	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Wrist fracture	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Surgical and medical procedures	**1 (1.2%)**	**1**	**1 (2.1%)**	**1**	**1 (1.3%)**	**1**	**3 (1.4%)**	**3**
Benign breast lump removal	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Intraocular lens implant	0	0	1 (2.1%)	1	0	0	1 (0.5%)	1
Cataract operation	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
General disorders and administration site conditions	**1 (1.2%)**	**1**	**0**	**0**	**1 (1.3%)**	**1**	**2 (1.0%)**	**2**
Inflammation	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Pyrexia	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1
Musculoskeletal and connective tissue disorders	**1 (1.2%)**	**1**	**0**	**0**	**1 (1.3%)**	**1**	**2 (1.0%)**	**2**
Jaw disorder	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Periarthritis	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1

System Organ Class/Preferred Term*	Active + Active N=81		Low amplitude control + Active N=47		Placebo + Active N=79		Total N=207	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Ear and labyrinth disorders	**1 (1.2%)**	**1**	**0**	**0**	**0**	**0**	**1 (0.5%)**	**1**
Eustachian tube dysfunction	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Endocrine disorders	**1 (1.2%)**	**1**	**0**	**0**	**0**	**0**	**1 (0.5%)**	**1**
Hypothyroidism	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.2%)**	**1**	**0**	**0**	**0**	**0**	**1 (0.5%)**	**1**
Prolactinoma	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Skin and subcutaneous tissue disorders	**1 (1.2%)**	**1**	**0**	**0**	**0**	**0**	**1 (0.5%)**	**1**
Swelling face	1 (1.2%)	1	0	0	0	0	1 (0.5%)	1
Reproductive system and breast disorders	**0**	**0**	**0**	**0**	**1 (1.3%)**	**1**	**1 (0.5%)**	**1**
Ovarian cyst	0	0	0	0	1 (1.3%)	1	1 (0.5%)	1

n = number of subjects, Percentages are based on the number of subjects within each treatment group, *Coded acc to MedDRA version 16.0E
Adverse events with partially missing start date were calculated as starting before second treatment

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