

Acupuncture for Nasal Congestion in Allergic Rhinitis

An Open-Label, Randomized, Monocenter Trial (ANCAR Trial)

Trial:	ANCAR Trial
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Table of contents

1.	Introduction	3
1.1.	Summary of changes	3
1.2.	Objectives	3
1.3.	Study design	3
1.4.	Sample size considerations	3
2.	Analysis time-points	3
2.1.	Multiplicity considerations	3
3.	Data included in the analysis.....	3
4.	Analysis reports	3
5.	General considerations for data analysis	4
5.1.	Analysis populations	4
5.2.	General analysis principles	4
6.	Study conduct and progress	4
6.1.	Baseline patient and disease characteristics.....	4
6.2.	Patient disposition.....	4
7.	Study drug exposure and compliance	4
8.	Efficacy analysis	5
8.1.	Primary endpoint:.....	5
8.2.	Secondary endpoints:	5
8.3.	Other analyses.....	6
9.	Safety and tolerability.....	8
9.1.	Adverse events (AEs)	8
10.	List of abbreviations	8

1. Introduction

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the analyses and overviews generated for the final analysis in the ANCAR trial as specified in the approved clinical study protocol.

No interim analysis beside the primary endpoint analysis were planned.

1.1. Summary of changes

Not applicable, this is the first final version of the SAP.

1.2. Objectives

The objectives of this analysis are efficacy in terms of VAS (Visual Analogue Scale), Adapted NOSE (Nasal Obstruction Symptom Evaluation), and PNIF (Peak Nasal Inspiratory Flow) improvement score, QOL (Quality of Life), and safety ((serious) adverse events).

1.3. Study design

The ANCAR trial is an open-label, randomized, monocenter trial.

1.4. Sample size considerations

The "Two-Sample Test for Proportions" design was applied for the sample size calculation based on the primary endpoint assumptions. i.e., by assuming incidence of 51.4% for arm A and the incidence of 18.1% for arm B - to compare these proportions and detect a difference with an alpha 0.05 two-tailed test, and a 80% statistical power - in total 62 patients (1:1 randomization) will be needed, of which 31 patients will be randomized to arm A and 31 patients to arm B. Please be referred to the ANCAR research protocol.

2. Analysis time-points

The analysis will be done when complete data on both treatment arms of all ITT (intention to treat) patients are available, cleaned and verified.

2.1. Multiplicity considerations

Not applicable.

3. Data included in the analysis

The analysis dataset will comprise all ITT patients in each arm, and will include all data up to the data cut-off date. The data cut-off date will be determined later, based on when these patients have completed the trial, or discontinued treatment prematurely, and when all relevant data have been cleaned and verified.

4. Analysis reports

The final report will be sent to the PI and Co-PI.

5. General considerations for data analysis

5.1. Analysis populations

The intention-to-treat (ITT) population is defined as all registered patients in each arm. All analyses will be based on ITT patients, unless explicitly stated otherwise.

5.2. General analysis principles

In the final analysis:

- Missing values will not be imputed;
- Discrete variables will be tabulated as numbers and percentages;
- Continuous variables will be summarized using mean+standard deviation (SD), median, inter-quartile range (IQR), range, number non-missing;
- If applicable, 95% confidence intervals (CIs) will be reported;
- One month is calculated as 30.4375 days, one year is calculated as 365.25 days;
- For the analyses the statistical package Stata (version 16.1 or higher) will be used.
- All questionnaire results will be converted to 0-100% scale by $(R-X)/R \times 100$ formula, where X is the average score, and R is maximum score in the Questionnaire.

6. Study conduct and progress

6.1. Baseline patient and disease characteristics

The baseline characteristics will be provided for all ITT patients by arm.

- Age at registration [year], Sex [male, female]

6.2. Patient disposition

The disposition of all ITT patients (in the specific arm) that started the therapy will be summarized in a "CONSORT" diagram that will include the number of patients who started therapy, the number of patients who completed and discontinued from treatment, along with the reason for treatment discontinuation reported in the CRF.

7. Study drug exposure and compliance

For all ITT patients (in the specific arm), the cycles will be described.

Data will be presented for each cycle separately based on the corresponding safety population, including:

- The number of patients that started treatment;
- The number of days between start of the current cycle as compared to start of the previous cycle.

8. Efficacy analysis

8.1. Primary endpoint:

Improvement of VAS score at 6 weeks

Definition: Defined as any decrease in VAS score (VAS questionnaire, Part A, question 1: Nasal congestion: see Appendix I in the protocol) at 6 weeks (visit 8) of treatments compared to the corresponding entry score (before starting treatment). The VAS score ranges between 0 to 10, where 0 = no nasal congestion, and 10 = most severe nasal congestion.

The formal test for difference in VAS improvement score after 6 weeks between the two treatment arms will be done with the two-sample proportions test, and the quantity of difference in VAS improvement will be summarized for each arm.

8.2. Secondary endpoints:

8.2.1. Improvement of VAS score in arm A (acupuncture)

Definition: Defined as any decrease in VAS score (VAS questionnaire, Part A, question 1: Nasal congestion: see Appendix I in the protocol) at visit 1, 2, ..., 10 of acupuncture treatments compared to corresponding entry score (before starting acupuncture treatment).

The VAS improvement score (and quantity of improvement) at visit 1, 2, ..., 10 of acupuncture treatments compared to entry VAS score over time will be summarized and graphically (Spaghetti plot) shown for each patient. A mixed-effects model will be used to analyze the trend of VAS score over time.

8.2.2. Improvement of VAS score in arm B (Azelastine Nasal Spray)

Definition: Defined as any decrease in VAS score (VAS questionnaire, Part A, question 1: Nasal congestion: see Appendix I in the protocol) at visit 1, 8, 9, 10 of Azelastine Nasal Spray treatments compared to corresponding entry score (before starting treatment).

The VAS improvement score (and quantity of improvement) at visit 1, 8, 9, 10 of Azelastine Nasal Spray treatments compared to corresponding entry score over time will be summarized and graphically (Spaghetti plot) shown for each patient. A mixed-effects model will be used to analyze the trend of VAS score over time.

8.2.3. Immediate improvement of VAS score in both arms

Definition: Defined as any decrease in VAS score (VAS questionnaire, Part A, question 1: Nasal congestion: see Appendix I in the protocol) before and after first treatment visit.

The VAS improvement score (and quantity of improvement) before and after first treatment visit will be summarized for each arm, separately. A paired t-test will be used to access the improvement of VAS score after treatment.

8.2.4. Improvement of PNIF score in both arms

Definition: Defined as any increase in PNIF score at visit 1, 8, 9, 10 of treatments compared to entry PNIF score (before starting treatment). The PNIF score ranges between 30 to 370 ml.

The PNIF improvement score (and quantity of improvement) at visit 1, 8, 9, 10 of treatments compared to corresponding entry score over time will be summarized and graphically (Spaghetti

plot) shown for each patient in each arm. A mixed-effects model will be used to analyze the trend of VAS score over time.

8.2.5. Immediate improvement of PNIF score in both arms

Definition: Defined as any increase in PNIF score before and after first treatment visit.

The PNIF improvement score (and quantity of improvement) before and after first treatment visit will be summarized for each arm, separately. A paired t-test will be used to assess the improvement of PNIF score after treatment.

8.2.6. Improvement of Adapted NOSE score in both arms

Definition: Defined as any decrease in Adapted NOSE score (NOSE questionnaire, Part A; average of questions 1-5: see Appendix II in the protocol) at visit 1, 8, 10 of treatments compared to the corresponding entry score (before starting treatment).

The Adapted NOSE improvement score (and quantity of improvement) at visit 1, 8, 10 of treatments compared to corresponding entry score over time will be summarized and graphically (Spaghetti plot) shown for each patient in each arm. A mixed-effects model will be used to analyze the trend of Adapted NOSE score over time.

8.3. Other analyses

8.3.1. To assess the effects of arm A (acupuncture) on other nasal signs and symptoms in AR based on VAS score.

Definition: Defined as any decrease in VAS score (VAS questionnaire, Part A, average questions 1-4, and 2-4: see Appendix I in the protocol) at visit 1, 2, ..., 10 of acupuncture treatments compared to the corresponding entry score (before starting acupuncture treatment).

The VAS improvement score (and quantity of improvement) at visit 1, 2, ..., 10 of acupuncture treatments compared to corresponding entry score over time will be summarized and graphically (Spaghetti plot) shown for each patient. A mixed-effects model will be used to analyze the trend of VAS score over time.

8.3.2. To assess the effects of arm B (Azelastine Nasal Spray) on other nasal signs and symptoms in AR based on VAS score.

Definition: Defined as any decrease in VAS score (VAS questionnaire, Part A, average questions 1-4, and 2-4: see Appendix I in the protocol) at visit 1, 8, 9, 10 of acupuncture treatments compared to the corresponding entry score (before starting acupuncture treatment).

The VAS improvement score (and quantity of improvement) at visit 1, 8, 9, 10 of acupuncture treatments compared to corresponding entry score over time will be summarized and graphically (Spaghetti plot) shown for each patient. A mixed-effects model will be used to analyze the trend of VAS score over time.

8.3.3. To assess the effects of arm A (acupuncture) on ocular signs and symptoms in AR based on VAS score.

Definition: Defined as any decrease in VAS score (VAS questionnaire, Part B, average questions 1-4: see Appendix I in the protocol) at visit 1, 2, ..., 10 of acupuncture treatments compared to the corresponding entry score (before starting acupuncture treatment).

The VAS improvement score (and quantity of improvement) at visit 1, 2, ..., 10 of acupuncture treatments compared to corresponding entry score over time will be summarized and graphically (Spaghetti plot) shown for each patient. A mixed-effects model will be used to analyze the trend of VAS score over time.

8.3.4. To assess the effects of arm B (Azelastine Nasal Spray) on ocular signs and symptoms in AR based on VAS score.

Definition: Defined as any decrease in VAS score (VAS questionnaire, Part B, average questions 1-4: see Appendix I in the protocol) at visit 1, 8, 9, 10 of acupuncture treatments compared to the corresponding entry score (before starting acupuncture treatment).

The VAS improvement score (and quantity of improvement) at visit 1, 8, 9, 10 of acupuncture treatments compared to corresponding entry score over time will be summarized and graphically (Spaghetti plot) shown for each patient. A mixed-effects model will be used to analyze the trend of VAS score over time.

8.3.5. To assess the immediate effects of treatment on other nasal signs and symptoms in AR based on VAS score.

Definition: Defined as any decrease in VAS score (VAS questionnaire, Part A, average questions 1-4, and 2-4: see Appendix I in the protocol) before and after first treatment visit.

The VAS improvement score (and quantity of improvement) before and after first treatment visit will be summarized for each arm separately. A paired t-test will be used to assess the improvement of VAS score after treatment.

8.3.6. To assess the immediate effects of treatment on ocular signs and symptoms in AR based on VAS score.

Definition: Defined as any decrease in VAS score (VAS questionnaire, Part B, average questions 1-4: see Appendix I in the protocol) before and after first treatment visit.

The VAS improvement score (and quantity of improvement) before and after first treatment visit will be summarized for each arm separately. A paired t-test will be used to assess the improvement of VAS score after treatment.

8.3.7. To assess the effects of treatment on general health, concentration and energy level in AR after different visits of treatments based on adapted NOSE score.

Definition: Defined as any decrease in Adapted NOSE score (NOSE questionnaire, Part B; average of questions 1-3: see Appendix II in the protocol) at visit 1, 8, 10 of treatments compared to the corresponding entry score (before starting treatment).

The adapted QOL improvement score (and quantity of improvement) at visit 1, 8, 10 of treatments compared to the corresponding entry score over time will be summarized and graphically (Spaghetti plot) shown for each patient for each arm. A mixed-effects model will be used to analyze the trend of QOL over time.

8.3.8. To assess the effects of treatment on equalization of middle ear pressure in AR in the case patients fly and/or dive after different visits of treatments based on Adapted NOSE score.

Definition: Defined as any decrease in Adapted NOSE score (NOSE questionnaire, Part C; average of questions 1-2: see Appendix II in the protocol) at visit 1, 8, 10 of treatments compared to the corresponding entry score (before starting treatment).

The equalization of middle ear pressure improvement score (and quantity of improvement) at visit 1, 8, 10 of treatments compared to the corresponding entry score over time will be summarized and graphically (Spaghetti plot) shown for each patient for each arm. A mixed-effects model will be used to analyze the trend of equalization of middle ear pressure score over time.

9. Safety and tolerability

9.1. Adverse events (AEs)

For all ITT patients in the specific arm, the number and percentage of patients with treatment adverse events (defined as any AEs, regardless of relationship to study drug) will be tabulated for each visit, as well as for all visits together.

10. List of abbreviations

Abbreviation	Term
AE	Adverse event
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
IQR	Inter-quartile range
ITT	Intention to treat
QOL	Quality of Life
NOSE	Nasal Obstruction Symptom Evaluation
PNIF	Peak Nasal Inspiratory Flow
SAE	Serious adverse event
SAP	Statistical analysis plan
SE	Standard error
VAS	Visual Analogue Scale