

RESEARCH PROTOCOL

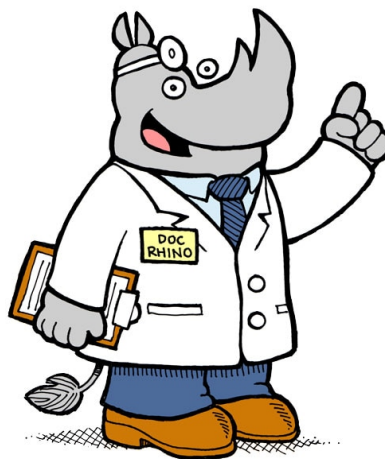
Acupuncture for Nasal Congestion in Allergic Rhinitis: An Open-Label, Randomized, Monocenter Trial (ANCAR Trial)

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PROTOCOL TITLE

Acupuncture for Nasal Congestion in Allergic Rhinitis: An Open-Label, Randomized, Monocenter Trial (ANCAR Trial)

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.

SUSAR	Suspected Unexpected Serious Adverse Reaction
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Allergic rhinitis (AR) is a disorder that affects more than 500 million people worldwide. Nasal congestion is one the most general and bothersome symptoms in rhinitis, which affects the quality of life (QOL). Current medications are undesirable due to their side-effects. Acupuncture for AR in general can be considered as safe and can be seen as a potential remedial blueprint for nasal congestion. Evidence supported that acupuncture is clinically used for signs and symptoms of nose disorders, such as nasal congestion, with effectiveness, but whether acupuncture has immediate, post-treatment and long-term effects on specifically nasal congestion in AR is not verified by strictly designed clinical study. The ANCAR trial uses a standard treatment protocol with a fixed set of acupuncture points - to be as scientific as possible from Western viewpoint - to open the nose and affect underlying energetic imbalance and immunity at the same time, to maintain its nose opening effect. This novel acupuncture treatment protocol can be seen as a solid and profound approach from which every AR patient may benefit.

Hypothesis: Acupuncture will improve nasal congestion in AR compare to azelastine nasal spray (Carelastin®).

Objective: To evaluate the effects of an acupuncture treatment protocol for nasal congestion in AR.

Study design: An open-label, randomized, monocenter trial.

Study population: Adult patients with AR sent to Mermaid Medicine® in The Hague, the Netherlands.

Intervention: The acupuncture arm will receive a fixed set of acupuncture points during 6 weeks: 2 treatments per week in the first 2 weeks and 1 treatment per week in the consecutive 4 weeks (10 acupuncture points with totally 17 needles per treatment). The control arm will receive Carelastin® azelastine nasal spray (1mg/1ml), 1 spray puff (0.14 ml) per nostril twice daily (0.56 mg totally per patient per day) during 6 weeks.

Main study parameters/endpoints: VAS, Adapted NOSE and PNIF.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Negligible risk.

1. INTRODUCTION AND RATIONALE

Worldwide more than approximately 500 million people suffer from AR^[1, 2] (30% of the Dutch population (Mylan Update, 2018^[2]) and its prevalence is expanding^[1]. Nasal congestion (i.e. reversible mucosal congestion^[3]/nasal mucosal obstruction^[4]) is one of the most general and bothersome symptoms in rhinitis^[5, 6] and is associated with other medical conditions such as rhinosinusitis and otitis media^[7, 8]. This study is relevant as in addition to the high global occurrence of AR, this disorder has substantial effects on the quality of life (QOL) (e.g. during sleep and work)^[9]. AR is related to high direct medical costs (mainly prescription of medications and outpatient visits) and indirect economic costs (including productivity decrease)^[8, 10, 11]. Current medications are undesirable due to their side-effects (such as sedation in the case of intranasal antihistamines (INAH)^[11]).

Acupuncture for AR in general can be considered as safe and can be seen as a potential remedial blueprint for nasal congestion^[12]. Evidence supported that acupuncture is clinically used for signs and symptoms of nose disorders, such as nasal congestion, with effectiveness, but whether acupuncture has immediate, post-treatment and long-term effects on specifically nasal congestion in AR is not verified by strictly designed clinical study.

The ANCAR trial aims to evaluate the effects of an acupuncture treatment protocol for nasal congestion in AR compare to azelastine nasal spray. A standard treatment protocol with a fixed set of acupuncture points has been established - to be as scientific as possible from Western medical viewpoint - and this selection of acupuncture points can be seen as a solid and profound approach from which every AR patient may benefit. This standard set opens the nose and affects the underlying energetic imbalance and immunity at the same time to maintain its nose opening effect (i.e. to prevent recurrence of the complaint).

The acupuncture protocol concerns 8 treatments during 6 weeks (i.e. 2 treatments per week during the first 2 weeks and 1 treatment per week in the consecutive 4 weeks).

The positive effects of this treatment protocol (such as improvement QOL), may result in more confidence in the direct, post-treatment and long-term effects of acupuncture and lead to more acceptance of acupuncture as a solid treatment option for nasal congestion in AR instead of using an INAH spray.

Hypothesis: Acupuncture will improve nasal congestion in AR compare to azelastine nasal spray (Carelastin®).

2. OBJECTIVES

Primary Objective:

- To compare the effects of acupuncture with azelastine nasal spray (Carelastin®) on nasal congestion in AR based on VAS (Visual Analog Scale) score.

Secondary Objectives:

- To compare the effects of acupuncture with azelastine nasal spray (Carelastin®) on nasal congestion in AR.
- To assess the effects of acupuncture on other nasal and ocular signs and symptoms in AR.

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- To assess the effects of acupuncture on general health, concentration and energy level in AR.
- To assess the effects of acupuncture on equalization of middle ear pressure in AR in the case patients fly and/or dive.

Primary endpoint:

- To compare the effects of acupuncture and azelastine nasal spray (Carelastin®) on nasal congestion in AR after 6 weeks of treatments based on VAS score (VAS questionnaire, Part A, question 1: Nasal congestion: see Appendix I). The VAS improvement score will be compared between two arms, improvement defined as any decrease in VAS score at 6 weeks of treatments compared to the corresponding entry VAS score (before starting treatment). VAS, 0 = no nasal congestion, and 10 = most severe nasal congestion.

Secondary endpoints:

- To compare the effects of acupuncture and azelastine nasal spray (Carelastin®) on nasal congestion in AR after different visits of treatments based on VAS, Adapted NOSE (Nasal Obstruction Symptom Evaluation (see Appendix II, part A)) and PNIF (Peak Nasal Inspiratory Flow) scores (PNIF: per clinical evaluation, 3 consecutive measurements are done to calculate the mean).
A PNIF meter (In-Check™) is used from GM Instruments® (measures nasal airflow during maximal inspiration with score ranges between 30 – 370 L/min) together with Intersurgical® masks (size Medium). The accuracy of the PNIF meter is: 10% or ± 10 L/min. Measuring: the PNIF test should be repeated 3 times and the highest score should be recorded in the patient's medical file. The PNIF meter is an inexpensive portable tool that estimates nasal congestion accurately and can be used to assess AR^[13]
The PNIF measurements procedure is as follows (according In-Check™ manual):
 - The patient will receive a face mask and the mouth must be closed.
 - In the case the patient wears glasses, they must be removed.
 - The patient is asked to:
 - exhale fully
 - hold the PNIF meter horizontally, and insure the mask forms an airtight seal around the nose
 - inhale forcibly through the nose (about 1 second duration).
- To assess the effects of acupuncture on other nasal and ocular signs and symptoms in AR based on VAS score (see Appendix I, part A-B).
- To assess the effects of acupuncture on general health, concentration and energy level in AR after different visits of treatments based on Adapted NOSE score (see Appendix II, part B).
- To assess the effects of acupuncture 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 (see Appendix II, part C).

3. STUDY DESIGN

- The trial is designed as an open-label, randomized, monocenter trial. All eligible patients will be randomized (1:1) between two arms (parallel assignment), i.e., arm A (Acupuncture) and arm B (Control [Carelastin®]).
- Short-Term-Intervention RCT: 6 weeks treatment protocol with measurements before and at 15 minutes after the 1st acupuncture treatment/1st azelastine usage (to compare the immediate effects), at 15 minutes after the 2nd - 8th acupuncture treatment and final usage of azelastine (= parallel to 8th acupuncture treatment = to compare the post-treatment effects), then following the treatment period after 2 weeks and 2 months (to compare the long-term effects). The accrual expected to be 60 days.

4. STUDY POPULATION

4.1 Population (base)

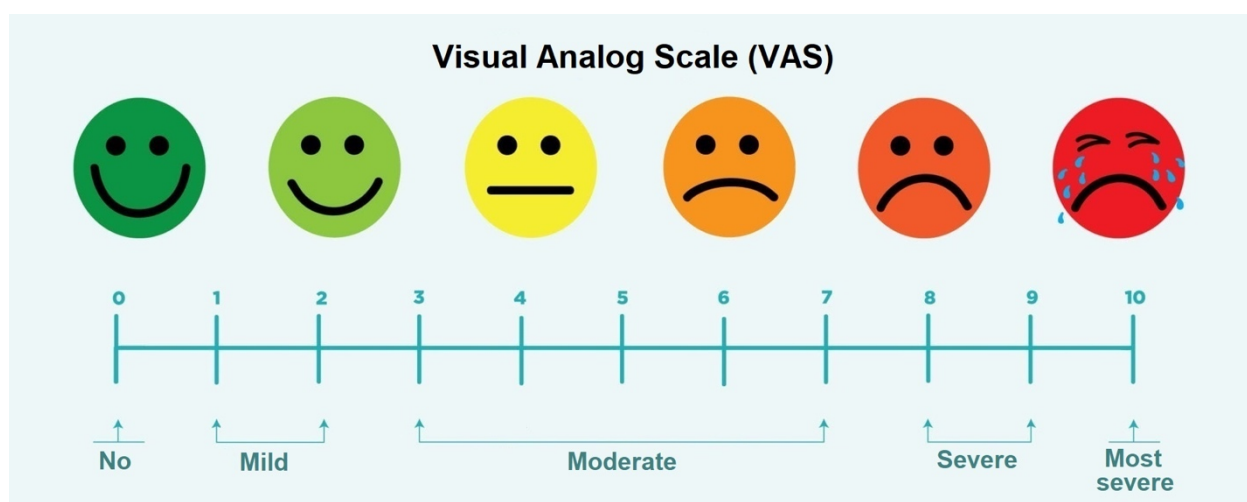
- Patients with AR that are sent to/visit Mermaid Medicine® during the recruitment (expected to be 60 days).

4.2 Inclusion criteria.

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Diagnosed AR by a physician.
- Have one of the AR types: seasonal (SAR) or perennial (PAR) or mixed (MAR) allergic rhinitis.
- VAS nasal congestion: from 3-10.
- Age: from 18 years.
- Signed Informed Consent.

Figure 4.2.1 VAS for the degree of nasal congestion^[14, 15] (and other nasal and ocular signs and symptoms)



VAS of 0 = no nasal congestion, and 10 = most severe nasal congestion.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- COVID-19.
- Acute common cold.
- Influenza.
- Fever (38°C or higher).
- Acute nasal trauma (such as a fracture and epistaxis).
- Irreversible nasal blockages (such as septum deviation, concha bullosa, polyps and cysts).
- Nasal and sinus cancer.
- Pregnancy or planning for pregnancy.
- Consumed decongestions, antihistamines, antibiotics or corticosteroids within 2 weeks before the RCT.
- Received acupuncture, Chinese herbal medicine or another complementary treatment within 2 weeks before the RCT.
- Received immunotherapy within 2 weeks before the RCT.
- Patients refusing or unable to sign Informed Consent.

4.4 Sample size calculation

East version 6.5 is used to calculate the sample size. The sample size is based on two independent study arms and the primary endpoint is dichotomous (yes/no).

Arm A has an incidence of 51.3% based on total nasal symptom score (TNSS) post-treatment of a SAR study from Xue et al. (2002, TNSS post-treatment of 66.3%) and a PAR study from Xue et al. (2007, TNSS post-treatment of 36.3%)^[16,17]. No exact information about nasal congestion of the SAR (2002) study is available and therefore the TNSS is used to calculate the sample size for the ANCAR trial. The use of azelastine (1 mg/ml, 1 spray of 14 mg in each nostril twice daily) in SAR has 14.1% and 22.1% improvement for the TNSS in respectively study 1 and study 2 from Lumry (2007)^[18], which results in a mean of 18.1% (= incidence arm B). There is no major difference between TNSS and VAS (there is a high correlation between TNSS and VAS). By estimating an incidence of 51.3% 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.

Sample size	
Arm A (Acupuncture)	Number dependent on randomization
Arm B (Control)	Number dependent on randomization
Total	62

Study parameters	
Incidence, arm A	51.3%
Incidence, arm B	18.1%
Alpha	0.05
Betha	0.2
Power	80%

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Acupuncture (Arm A)

A fixed set of acupuncture points is used for every patient. The RCT treatment concerns 10 acupuncture points per treatment (= totally 17 needles per treatment).

In total 8 acupuncture treatments: 2 treatments per week during the first 2 weeks and 1 treatment per week in the consecutive 4 weeks.

LI-20 (Yingxiang -) *bilateral*, Bitong (**M-HN-14** -) *bilateral*, Yintang (**M-HN-3** -) *on midline body*, **GV-23** (Shangxing -) *on midline body*, **LI-4** (Hegu -) *bilateral*, **LU-7** (Lieque -) *bilateral*, **CV-6** (Qihai +) *on midline body*, **ST-36** (Zusanli +) *bilateral*, **SP-6** (Sanyinjiao +) *bilateral*, Ear: Allergy Point (-) *bilateral*.

+ = Tonifying needling technique, - = Reducing needling technique

Needles

- Standard disposable sterile acupuncture needles.
- Brand needles: Cloud & Dragon (DocSave.com).
- Needle sizes: on the face: size: 0.22 x 25 mm, on the belly and limbs: 0.25 x 40 mm, for Ear Apex Allergy Point: 0.22 x 15 mm.

Needling Specifications

- Needling time: 30 minutes.
- Needle sensation (Deqi). Deqi is defined (according the latest Chinese-English Dictionary of Traditional Chinese Medicine (TCM)^{[19][pp.877-878]}) as 'needling sensation, which refers to the patient's response to sore, numb, distention, electric shock and the doctor's heavy and tight sensation coming from beneath the needle'.

Azelastine Nasal Spray (Arm B)

Carelastin® is used with the conventional dosage (= most generally recommended dosage):

1 spray puff per nostril twice daily^[18]. 1 spray puff (0.14 ml) of Carelastin® (1 mg/ml) contains 0.14 mg (137 mcg) azelastine hydrochloride (0.56 mg totally per patient per day).

5.2 Use of co-intervention (if applicable)

- Acupuncture arm: No oral or intranasal decongestions, antihistamines or corticosteroids.

- Azelastine arm: No other INAH, no oral antihistamines and no oral or intranasal decongestions or corticosteroids.

5.3 Escape medication (if applicable)

Not applicable.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)/treatment

- Acupuncture.

6.2 Summary of findings from non-clinical studies

Not applicable.

6.3 Summary of findings from clinical studies

Acupuncture can be seen as a potential remedial blueprint for nasal congestion, especially in the case of non-efficacy, drug resistance or atrophic rhinitis^[12].

Acupuncture could be a valid and effective treatment option for signs and symptoms of AR^[20,21] with an efficacious improvement of QOL^[21]. However: a standard treatment protocol and a standardized scoring system (high-quality research^[22]) are missing^[20]. The ANCAR trial - consisting of a complete, compact and fixed set of acupuncture points - may contribute to a clear and effective treatment protocol for nasal congestion in AR.

Clinical note: Additional information regarding the efficacy of acupuncture for complaints of allergic rhinitis, which substantiates the statements in this summary, is added as Appendix IV.

6.4 Summary of known and potential risks and benefits

Acupuncture for AR in general can be considered as safe^[20,21]. No fatal or serious events are reported^[20,21], solely mild side-effects such as pain, papules, pruritus, subcutaneous hematomas, dizziness, numbness and headache^[20].

Benefits: acupuncture can reduce signs and symptoms of AR^[20, 21], has the possibility to boost blood rheology indexes with an increased volume of blood circulation and regulation of immunity^[23] besides that there is evidence of reduction of the plasmatic level of IL-10 in chronic AR patients^[24], efficacious improvement QOL^[21].

6.5 Description and justification of route of administration and dosage

- 8 acupuncture treatments during 6 weeks. 2 treatments per week in the first 2 weeks and 1 treatment per week in the consecutive 4 weeks.
- Needling retention time: 30 minutes.
- Needling depth: It needs to meet the requirements of acupuncture theory, human physiology and individual difference (the different acupuncture points require different needling depth).

6.6 Dosages, dosage modifications and method of administration

- Reducing needling technique is used for: **LI-20** (Yingxiang), Bitong (**M-HN-14**), Yintang (**M-HN-3**), **GV-23** (Shangxing), **LI-4** (Hegu), **LU-7** (Lieque) and Ear: Allergy Point.
- Tonifying needling technique is used for: **CV-6** (Qihai), **ST-36** (Zusanli) and **SP-6** (Sanyinjiao).

Table 6.6 Needling techniques^{[25][p.40]}

Reinforcing (Tonifying/+) Method	Reducing (Sedating/-) Method
Lifting and thrusting: Lifting the needle gently and slowly; thrusting heavily and rapidly	Lifting and thrusting: Lifting the needle forcefully and rapidly; thrusting gently and slowly
Twirling and rotating: Rotating gently and slowly with small amplitude	Twirling and rotating: Rotating rapidly with large amplitude
Rotating direction: Clockwise	Rotating direction: Counter-clockwise
Insertion: Slow	Insertion: Rapid
Withdrawal: Rapid	Withdrawal: Slow
Direction tip of the needle: Following the direction of the course of the channel	Direction tip of the needle: Against the direction of the course of the channel
Keeping the hole open or closed: Press the hole rapidly (to prevent that Qi escapes)	Keeping the hole open or closed: Shake it to enlarge the hole (to drive out Xie Qi)
Respiration: Inserting the needle when the patient breathes out, withdrawing when breathing in	Respiration: Inserting the needle when the patient breathes in, withdrawing when breathing out

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable.

6.8 Drug accountability

Not applicable.

7. NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

- Carelastin[®] nasal spray (1 mg/ml).

7.2 Summary of findings from non-clinical studies

Not applicable.

7.3 Summary of findings from clinical studies

- Azelastine nasal spray (0.1%) monotherapy has clinical efficacy for treating AR that is equal or superior to oral second-generation antihistamine, has a clinically significant effect on nasal congestion^[26,27,28] and can be used on an as needed

basis compare to INCS that need to be taken before the symptoms start to benefit optimally from its effects^[28]. Intranasal antihistamines (INAH) have a quicker onset of action compare to intranasal corticosteroids (INCS)^[29] (e.g. azelastine nasal spray tested superior to mometasone nasal spray^[30]).

- Azelastine nasal spray is also approved for non-allergic rhinitis (NAR)^[26] and equally effective (with 2 sprays per nostril twice daily, 1.1 mg/day) as the combination therapy of oral loratadine (Claritin®, one 10-mg tablet/day) and intranasal beclomethasone (INCS) (i.e. Beconase AQ®, 2 sprays per nostril twice daily, 336 mcg/day) treating moderate to severe SAR (both early-phase and late-phase signs and symptoms)^[27].
- Azelastine nasal spray (1 spray puff per nostril twice daily (= totally 0.28 mg per nostril/day)) is effective and has better tolerability compared to 2 sprays per nostril twice daily (= totally 0.56 mg per nostril/day) in moderate-severe SAR patients^[18] and has been proved effective and safe in the treatment of moderate-severe PAR^[31].
- Globally, azelastine nasal spray is approved for SAR and PAR treatment in more than 80 countries^[18].

7.4 Summary of known and potential risks and benefits

- Side-effects: bitter taste, drowsiness^[11, 27], headache and nasal burning^[27].
- Benefits: quick onset of action: at 15 minutes in SAR^[32] and PAR^[31] and last up to 4 hours^[33]/12 hours^[34].

7.5 Description and justification of route of administration and dosage

- 1 spray puff (0.14 ml) of Carelastin® (1 mg/ml) contains 0.14 mg (137 mcg) azelastine hydrochloride. 1 spray puff per nostril twice daily (totally 0.28 mg per nostril / total dosage of 0.56 mg per day) is the conventional (= most generally recommended) dosage for AR and is effective and has better tolerability compared to 2 spray puffs twice daily (totally 0.56 ml per nostril) in moderate-severe SAR patients^[18] and has been proved effective and safe in the treatment of Chinese patients with moderate-severe PAR^[31].

7.6 Dosages, dosage modifications and method of administration

- Dosages, dosage modifications: 1 spray puff in each nostril twice daily.
- Method of administration: Spray (with pump)
 - When using the spray for the first time, you have to press the pump a few times until a fine mist comes out. The spray chamber then can fill with the solution. The next time this is no longer necessary.
 - Blow the nose beforehand.
 - Shake the bottle several times to mix the contents.
 - Keep your head upright, insert the tip of the nose piece into one nostril, keep the other nostril closed and press the pump once. Sniff the liquid simultaneously so that the medicine enters deep into the nose.
 - Do not swallow the excess mucus, but spit it out.
 - Rinse and dry the spray head after use.

7.7 Preparation and labelling of Non-Investigational Medicinal Product

- Original Carelastin® nasal spray.

7.8 Drug accountability

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

- VAS to compare the effects of acupuncture with azelastine nasal spray (Carelastin®) on nasal congestion in AR after 6 weeks of treatments (VAS, 0 = no nasal congestion, and 10 = most severe nasal congestion). The VAS score improvement defined as any decrease in VAS score at 6 weeks of treatments compared to entry VAS score (before starting treatment).

8.1.2 Secondary study parameters/endpoints (if applicable)

- Adapted NOSE and PNIF to compare the effects of acupuncture with azelastine nasal spray (Carelastin®) on nasal congestion in AR after different visits of treatments. In terms of improvement and the quantity of improvement.
- VAS to assess the effects of acupuncture on other nasal and ocular signs and symptoms in AR (sneezing, nasal itching, rhinorrhea, itchy eyes, red eyes, burning eyes and watery eyes).
- Adapted NOSE with novel additions regarding general health, concentration, energy level and ear pressure equalization in diving and flying.

8.1.3 Other study parameters (if applicable)

Not applicable.

8.2 Randomization, blinding and treatment allocation

- The 1:1 randomization to arm A and B with block randomization size of 2 and 4 will be done by an independent statistician via a computer program (R program language blockrand package). The 62 randomly generated treatment allocations will be sent in advance within sealed opaque envelopes to the Mermaid Medicine site. Once a patient has consented to enter the trial, and after controlling the eligibility criteria the assigned envelope will be opened and the patient is then offered the allocated treatment regimen.

8.3 Study procedures

Time of clinical evaluations

- **T0:**
At entry: Controlling the eligibility of patients by including and excluding criteria. Providing information, Informed Consent and taking medical history (health profile including TCM pulse and tongue diagnosis). After patient inclusion the patient will be assigned to the randomly assigned arm.

- **T1:**
T1_1 = Before 1st acupuncture treatment/1st usage of Carelastin® azelastine nasal spray (VAS, Adapted NOSE, PNIF).
T1_2 = At 15 minutes after 1st acupuncture treatment/1st usage of Carelastin® azelastine nasal spray (VAS, PNIF, adverse effects (AEs), remarks patient).
- **T2:**
Only for arm A: At 15 minutes after acupuncture treatments 2-7 (VAS, AEs, remarks patient).
- **T3:** Primary endpoint
At 15 minutes after acupuncture treatment 8/final usage Carelastin® azelastine nasal spray (VAS, Adapted NOSE, PNIF, AEs, remarks patient).
- **T4:**
After 2 weeks after the 6 weeks treatment protocol (for both arms): VAS, PNIF, AEs, remarks patient.
- **T5:**
After 2 months after the 6 weeks treatment protocol (for both arms): VAS, Adapted NOSE, PNIF, AEs, remarks patient.

All patients will be followed until 2 months after registration and at every visit if the patient has COVID-19, the common cold, influenza, fever or suspected to have COVID-19, the common cold or influenza, the visit will be postponed and this will be considered as protocol violation.

Table. Details Timeline of the ANCAR trial

	T0 At entry	T1_1	T1_2	T2 Only for arm A (Acupuncture 2:7)	T3 Primary endpoint (end of treatment)	T4 2 weeks follow UP	T5 2 months follow UP
Inclusion and exclusion criteria	X						
Informed consent	X						
Medical history	X						
TCM pulse and tongue diagnosis	X						
VAS		X ¹	X ¹	X ^{1, 2}	X ¹	X ¹	X ¹
Adapted NOSE		X			X		X
PNIF		X	X		X	X	X
Adverse events (AEs)			X	X ²	X	X	X
Remarks patient			X	X ²	X	X	X

¹ At every visit the patient will be asked/examined for having COVID-19, the common cold, influenza, or fever. In case of positive result, the visit will be postponed.

² Only for arm A at 15 minutes after Acupuncture visits 2 till 7.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons or pregnancy.

If the patient has COVID-19, the common cold, influenza, fever or suspected to have COVID-19, the common cold or influenza, the visit will be postponed.

8.4.1 Specific criteria for withdrawal (if applicable)

- The patient is sick and can't come to Mermaid Medicine to participate the ANCAR trial.
- The patient does not want to participate the ANCAR trial anymore.
- The patient does not feel well during the treatment and does not finish the ANCAR trial.
- The patient moves away during the ANCAR trial.

8.5 Replacement of individual subjects after withdrawal

Not applicable. The trial will be performed based on ITT principle.

8.6 Follow-up of subjects withdrawn from treatment

Withdrawn patient will be considered as failure for primary endpoint and won't be followed up further.

8.7 Premature termination of the study

The study might be prematurely terminated based on the following criteria:

- There is evidence of an unacceptable risk for study patients (i.e. safety issue).
- There is reason to conclude that it will not be possible to collect the data necessary to reach the study objectives and it is therefore not ethical to continue enrollment of more patients (for example insufficient enrollment that cannot be improved).

9.SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

- Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

- All adverse events will be reported.

9.2.2 Serious adverse events (SAEs).

- No serious adverse events are expected with the use of azelastine and acupuncture.
- Adverse events of azelastine: bitter taste, drowsiness^[11, 27], headache and nasal burning^[27].
- Acupuncture for AR in general can be considered as safe^{[20][21]}. No fatal or serious events are reported^[20,21], solely mild side effects such as pain, papules, pruritus, subcutaneous hematomas, dizziness, numbness and headache^[20].

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

Not applicable.

10. STATISTICAL ANALYSIS

All main analyses will be according the intention to treat (ITT) principle. Patients will be analyzed according to the treatment arm they were assigned/randomized to. The formal test for difference between the two treatment arms will be done with the two-sample proportions test. Patients who achieve a response after 6 weeks will be considered as a success. All other patients will be considered as a failure, including patients going off protocol before evaluation (6 weeks) whatever the cause. Besides we will calculate the proportion difference and its 95% confidence interval. This analysis will not be performed when the data have been validated.

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;

A separated statistical analysis plan (SAP) will be provided to describe all analyses in details.

10.1 Primary study parameter(s)

- The VAS improvement score will be compared between two arms, improvement defined as any decrease in VAS score at 6 weeks of treatments compared to entry VAS score (before starting treatment). (VAS, 0 = no nasal congestion, and 10 = most severe nasal congestion)

10.2 Secondary study parameter(s)

- The VAS, PNIF and Adapted NOSE scale improvement score will be assessed at different visits as described in the table of timeline.

10.3 Other study parameters

- The effects of acupuncture on other nasal and ocular signs and symptoms, on general health, concentration and energy level, and equalization of middle ear pressure in AR will be assessed at different visits as described in the table of timeline.

10.4 Interim analysis (if applicable)

Not applicable. No interim analysis has been designed.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The ANCAR trial will be conducted according to the principles of the Declaration of Helsinki of 1975 (version 9, July 9, 2018) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

Patients will be recruited by sending emails to practices of general practitioners, besides ENT physicians and allergists in hospitals in the direct surroundings of Mermaid Medicine in Den Haag, the Netherlands. The patients will have 1 week to decide if they want to participate the ANCAR Trial.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

11.4 Benefits and risks assessment, group relatedness

Participation in the study has a negligible risk. Acupuncture for AR in general can be considered as safe^[20,21]. No fatal or serious events are reported^[20,21], solely mild side-effects such as pain, papules, pruritus, subcutaneous hematomas, dizziness, numbness and headache^[20].

Side-effects Carelastin® azelastine nasal spray: bitter taste, drowsiness^[11, 27], headache and burning sensation in the nose^[27].

Benefits: Acupuncture and Carelastin® azelastine nasal spray can reduce AR symptoms.

11.5 Compensation for injury

A request for an insurance waiver is included (test subject insurance).

Mermaid Medicine®/Johanna Maria Vermeulen has a professional liability insurance paramedics with the VvAA (policy number 11859873).

11.6 Incentives (if applicable)

During the ANCAR trial, patients in arm A will receive 8 acupuncture treatments and patients in arm B will get 2 Carelastin® nasal sprays. All treatment will be given to patients free of charge. If the results are positive (arm A is superior vs arm B), the patients in arm B also will receive discounts on 8 acupuncture treatments (25 € discount per session) at Mermaid Medicine during 1 year after the ANCAR trial. The patients from arm B must complete the 6-weeks treatment protocol and follow-up measurements to receive this discount.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data will be stored in Excel file on laptop from the sponsor/researcher. The results of the ANCAR trial will be shared safely with dr. Kazem Nasserinejad, statistician, who will analyze the results of this RCT. No other people or NJUCM will get this information.

The contact details of dr. Kazem Nasserinejad:

Phone: +31 (0) 64 2422405.

E-mail: info@consultistics.nl.

Website: <https://www.consultistics.nl/>.

12.2 Monitoring and Quality Assurance

Not applicable.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The sponsor is the investigator.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

See mentioned above (9.2.2) adverse events of azelastine nasal spray. Azelastine nasal spray is investigated and well-known already.

a. Level of knowledge about mechanism of action

Not applicable.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

Not applicable.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Not applicable.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Not applicable.

e. Analysis of potential effect

Not applicable.

f. Pharmacokinetic considerations

Not applicable.

g. Study population

Not applicable.

h. Interaction with other products

Not applicable.

i. Predictability of effect

Not applicable.

j. Can effects be managed?

Not applicable.

13.2 Synthesis

Not applicable.

Appendix I: VAS – Score

14. Appendixes

VAS – Score ‘Acupuncture for Nasal Congestion in Allergic Rhinitis’ – 2022

‘Acupunctuur voor Verstopte Neus bij Allergische Rhinitis’ – 2022

Date:

Date:

Participant number:

Deelnemersnummer:

- **To the participant: Please help us to better understand the severity of your nasal and ocular symptoms by completing the following survey (parts A and B).**

Thank you!

Aan de deelnemer: Help ons a.u.b. om de ernst van uw neus- en oogsymptomen beter te begrijpen door de volgende vragenlijst (delen A en B) in te vullen.

Dank u wel!

A.) Nasal Symptoms

Neussymptomen

Please circle the number between 0 and 10 that describes your symptom.

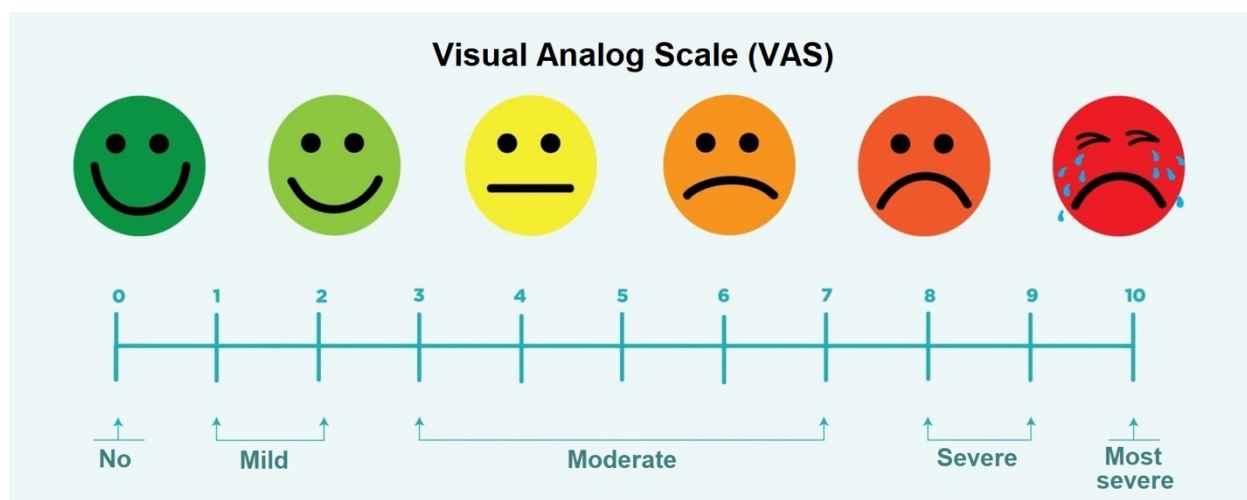
Omcirkel alstublieft het getal tussen 0 en 10 dat uw symptoom omschrijft.

0 = No symptom (e.g. no nasal congestion).

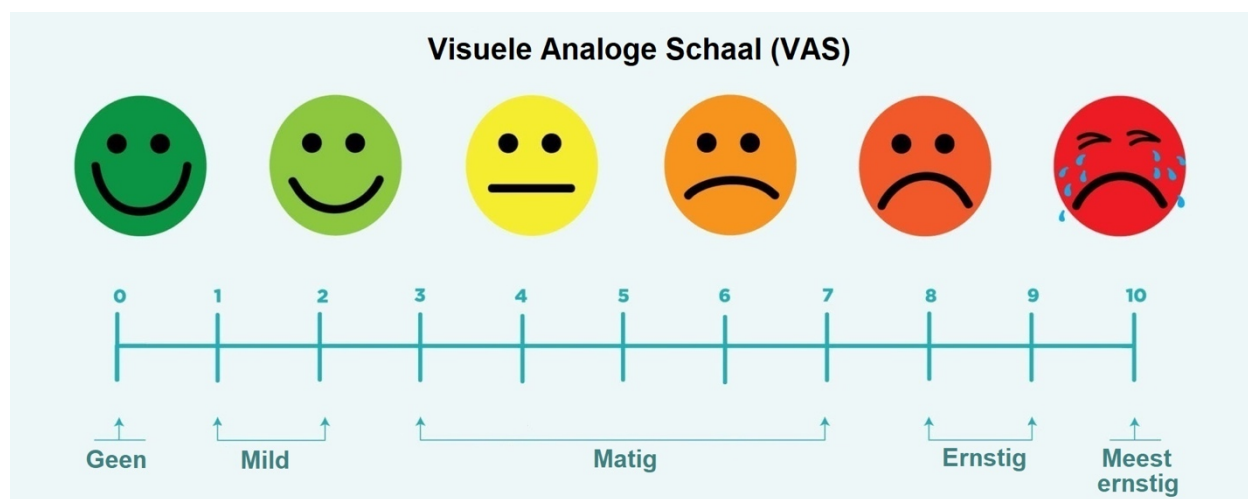
Geen symptoom (bijv. geen verstopte neus).

10 = Most severe symptom (e.g. most severe nasal congestion)

Meest ernstige symptoom (bijv. meest ernstige verstopte neus).



Appendix I: VAS – Score



1. Nasal Symptoms

Neussymptomen

	No symptom <i>Geen symptoom</i>					Most severe symptom <i>Meest ernstige symptoom</i>					
Nasal congestion <i>Verstopte neus</i>	0	1	2	3	4	5	6	7	8	9	10
Sneezing <i>Niezen</i>	0	1	2	3	4	5	6	7	8	9	10
Nasal itching <i>Jeukende neus</i>	0	1	2	3	4	5	6	7	8	9	10
Rhinorrhea <i>Loopneus</i>	0	1	2	3	4	5	6	7	8	9	10

Appendix I: VAS – Score

2. Ocular Symptoms

Oogsymptomen

Please circle the number between 0 and 10 that describes your symptom.

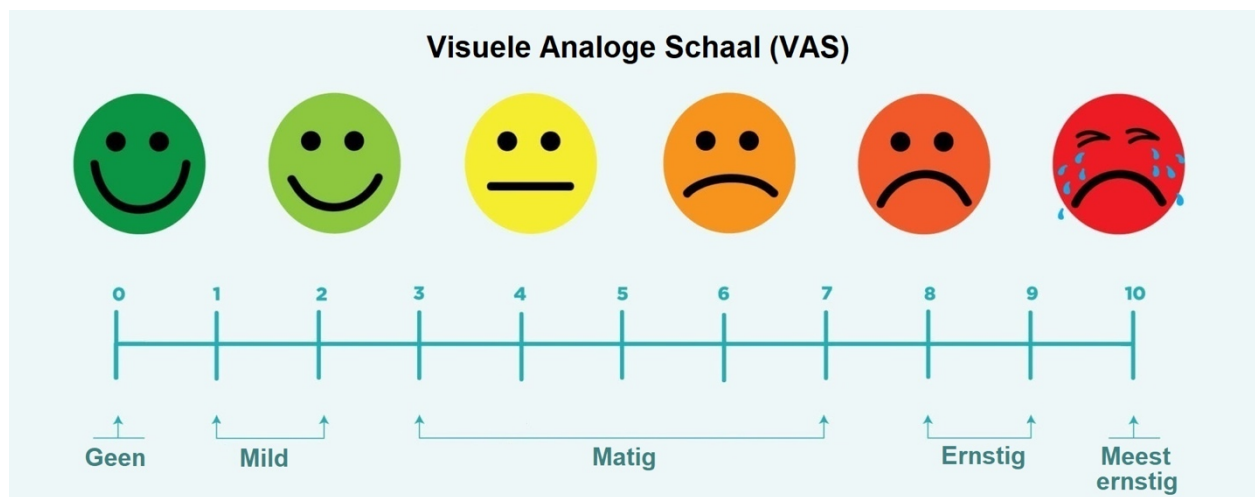
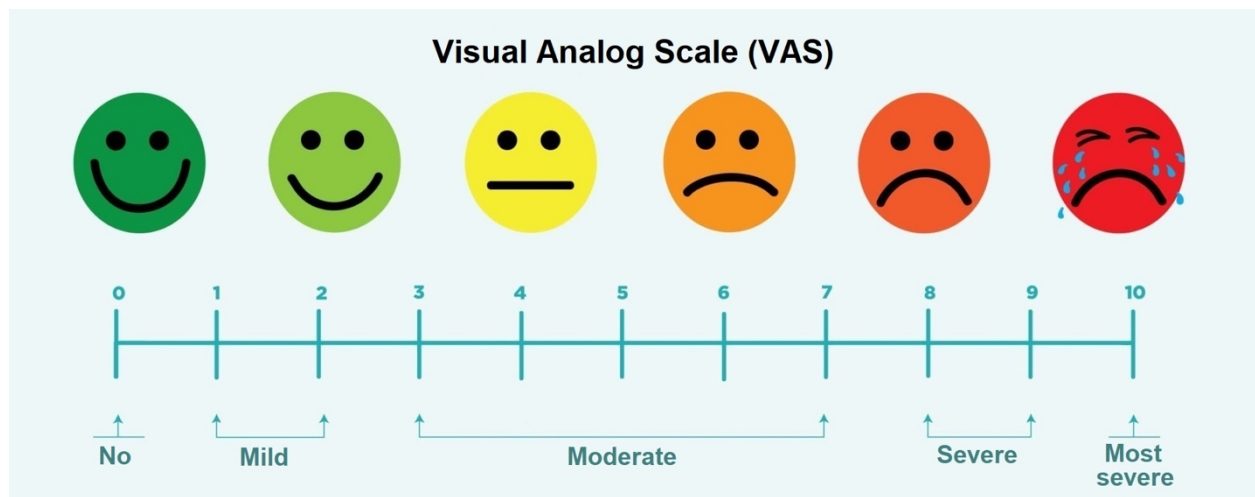
Omcirkel alstublieft het getal tussen 0 en 10 dat uw symptoom omschrijft.

0 = No symptom (e.g. no itchy eyes).

Geen symptoom (bijv. geen jeukende ogen).

10 = Most severe symptom (e.g. most severe itchy eyes).

Meest ernstige symptoom (bijv. meest ernstige jeukende ogen).



Appendix I: VAS – Score

	No symptom <i>Geen symptoom</i>										Most severe symptom <i>Meest ernstige symptoom</i>
Itchy eyes <i>Jeukende ogen</i>	0	1	2	3	4	5	6	7	8	9	10
Red eyes <i>Rode ogen</i>	0	1	2	3	4	5	6	7	8	9	10
Burning eyes <i>Brandende ogen</i>	0	1	2	3	4	5	6	7	8	9	10
Watery eyes <i>Tranende ogen</i>	0	1	2	3	4	5	6	7	8	9	10

Appendix II: Adapted NOSE Scale

Adapted NOSE Scale 'Acupuncture for Nasal Congestion in Allergic Rhinitis' - 2022

'Acupunctuur voor Verstopte Neus bij Allergische Rhinitis' – 2022'

Date:

Datum:

Participant number:

Deelnemersnummer:

- **To the participant: Please help us to better understand the impact of nasal obstruction on your quality of life by completing the following survey (parts A, B and C).**

Thank you!

Aan de deelnemer: Help ons a.u.b. om de impact van de neusobstructie op uw kwaliteit van leven beter te grijpen door de volgende vragenlijst (delen A, B en C) in te vullen.

Dank u wel!

A.) NOSE Scale.

NOSE Vragenlijst.

Over the past one month, how much of a problem were the following conditions for you?

In hoeverre waren de volgende situaties de afgelopen maand een probleem voor u?

Please circle the most correct response.

Omcirkel alstublieft het best passende antwoord.

	Not a problem <i>Geen problem</i>	Very mild problem <i>Licht probleem</i>	Moderate problem <i>Matig probleem</i>	Fairly bad problem <i>Redelijk ernstig probleem</i>	Severe problem <i>Ernstig probleem</i>
Nasal congestion or stuffiness <i>Verstopte neus of vol gevoel</i>	0	1	2	3	4
Nasal blockage or obstruction	0	1	2	3	4

Appendix II: Adapted NOSE Scale

<i>Neusblokkade of obstructie</i>					
Trouble breathing through my nose <i>Moeite met ademen door de neus</i>	0	1	2	3	4
Trouble sleeping <i>Moeite met slapen</i>	0	1	2	3	4
Unable to get enough air through my nose during exercise or exertion <i>Niet voldoende lucht door de neus krijgen bij sport of inspanning</i>	0	1	2	3	4

B.) General Addition.

Algemene Aanvulling.

Please circle the most correct response.

Omcirkel alstublieft het best passende antwoord.

	Excellent <i>Uitstekend</i>	Very good <i>Heel goed</i>	Good <i>Goed</i>	Fair <i>Redelijk</i>	Poor <i>Slecht</i>
How is your general health? <i>Hoe is uw gezondheid in het algemeen?</i>	0	1	2	3	4

Appendix II: Adapted NOSE Scale

How is your concentration? <i>Hoe is uw concentratie?</i>	0	1	2	3	4
How is your energy level? <i>Hoe is uw energieniveau?</i>	0	1	2	3	4

C.) Specific Addition Diving and Flying.

Specifieke Aanvulling Duiken en Vliegen.

Over the past one month, how much of a problem were the following conditions for you?

In hoeverre waren de volgende situaties de afgelopen maand een probleem voor u?

In the case you did not dive or fly, please answer: 'Not applicable (99)'.

In het geval u niet dook of vloog, antwoord a.u.b: 'Niet van toepassing (99)'.

Please circle the most correct response.

Omcirkel alstublieft het best passende antwoord.

Not a problem
Geen problem

Very mild problem
Licht problem

Moderate problem
Matig Probleem

Fairly bad problem
Redelijk ernstig probleem

Severe problem
Ernstig probleem

Not applicable
Niet van toepassing

Equalizing pressure of the ears while diving <i>Klaren van de oren tijdens duiken</i>	0	1	2	3	4	99
Equalizing pressure of the						

Appendix II: Adapted NOSE Scale

ears while flying <i>Klaren van de oren tijdens vliegen</i>	0	1	2	3	4	99
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Appendix III: Working Schedule ‘Acupuncture for Nasal Congestion in Allergic Rhinitis’ – 2023

INTAKES	WEEK 1			WEEK 2	WEEK 3	WEEK 4
1-17 May	Acu 1	Spray 1	Acu 2	Acu 3	Acu 4	Acu 5
	22-23 May	24 May	25-26 May	30-31 May	1-2 June	8-9 June
						15-16 June

WEEK 5	WEEK 6	Follow UP 1	Follow UP 2
Acu 7	Final spray	Acu 8	Spray
22-23 June	28 June	29-30 June	12 July
			13-14 July
			30 August
			31 August-1 September

INTAKES	WEEK 1			WEEK 2	WEEK 3	WEEK 4
	Acu 1	Spray 1	Acu 2	Acu 3	Acu 4	Acu 5
June-July-August	4 September	6 September	7 September	11 September	14 September	21 September
						28 September

WEEK 5	WEEK 6	Follow UP 1	Follow UP 2
Acu 7	Final spray	Acu 8	Spray
5 October	11 October	12 October	25 October
			26 October
			13 December
			14 December

INTAKES	WEEK 1			WEEK 2	WEEK 3	WEEK 4
	Acu 1	Spray 1	Acu 2	Acu 3	Acu 4	Acu 5
January-February 2024	4 March	6 March	7 March	11 March	14 March	21 March
						28 March

WEEK 5	WEEK 6	Follow UP 1	Follow UP 2
Acu 7	Final spray	Acu 8	Spray
4 April	10 April	11 April	24 April
			25 April
			12 June
			13 June

Appendix IV: Additional Scientific Research regarding Efficacy of Acupuncture for Complaints of Allergic Rhinitis

Acupuncture may induce anti-inflammatory effects in AR^[35] (including antihistamine effects (reduction of histamine-induced itch is proven in healthy subjects^[36, 37, 38]), and downregulation of proinflammatory neuropeptides substance P (SP) and vasoactive intestinal peptide (VIP), which is associated with improvements in AR signs and symptoms^[39]).

There are two small studies (i.e. Heidelberg studies, consisting of one single treatment to measure the immediate effect of acupuncture) that are focused on nasal congestion (due to hypertrophic inferior turbinates or chronic rhinosinusitis without polyposis in 2009 with 24 participants^[12] and due to hypertrophic inferior turbinate as a result of allergic and chronic rhinitis in 2015 with 25 participants^[40]).

The first Heidelberg study (2009) was not performed properly as the control (sham acupuncture) group used specific acupuncture points (such as GV-20 (Baihui) which can be used for nasal obstruction and nasal discharge) but they were mentioned to be non-specific points (control acupuncture showed an improvement in VAS but a decrease of nasal air flow (NAF)^[12]). Verum acupuncture was significant in improving VAS and NAF but less than xylometazoline^[12].

The second Heidelberg study (2015) used points in the control (sham) acupuncture group that were not representing existing points but control acupuncture delivered better results than expected^[40]. Both Heidelberg studies were not focused on nasal congestion in exclusively AR and not performed longer to measure long-term effects as well. Both studies used sham acupuncture in the control arms, which is no real (not a valid) placebo treatment^[41, 42] (sham acupuncture is considered as an active placebo, also called minimal acupuncture^[43]).

One Korean study (2005) examined nasal obstruction in persistent allergic rhinitis after one single acupuncture treatment but also used sham acupuncture for the control arm. The conclusion was that acupuncture improved nasal obstruction but that further research is needed to observe the long-term effect^[44].

There are acupuncture studies focused on AR in general, which show its effectiveness such as AR studies from B. Brinkhaus (2008^[45], ACUSAR trial in 2010^[46]) but these trials did not work with a totally fixed set of acupuncture points for every patient (but with an individual treatment per patient according Chinese medicine principles, which is seen as less scientific from Western viewpoint). The Brinkhaus trials used sham acupuncture in one of the control arms (while referring it is no placebo^[46]). The ACUSAR trial showed that acupuncture is effective improving the QOL in SAR patients^[47].

In AR studies from for example Choi (2013)^[48] and Xue (2002, 2007)^[17, 16] sham acupuncture was used as well in (one of) the control group (s) but sham acupuncture is no real placebo treatment^[42, 43].

However, none of these mentioned studies were specifically focused on nasal congestion in AR and/or using a strictly designed protocol.

15. REFERENCES

1. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(8):8-160. doi:10.1111/j.1398-9995.2007.01620.x
2. Website M. Allergische rhinitis. Updated November 13, 2018. Accessed December 3, 2021. <https://www.mylan.nl/nl-nl/therapeutische-gebieden/allergische-rhinitis>
3. Kjaergaard T, Cvancarova M, Steinsvag SK. Nasal congestion index: A measure for nasal obstruction. *Laryngoscope*. 2009;119(8):1628-1632. doi:10.1002/lary.20505
4. Ichimura K. Mechanism of nasal obstruction in patients with allergic rhinitis. *Clin Exp Allergy*. 2010;10(1):20-27. <https://doi.org/10.1111/j.1472-9733.2010.01151.x>
5. Lieberman P, Kaliner MA, Wheeler WJ. Open-label evaluation of azelastine nasal spray in patients with seasonal allergic rhinitis and nonallergic vasomotor rhinitis. *Curr Med Res Opin*. 2005;21(4):611-8. doi:10.1185/030079905X41408
6. Craig TJ, Sherkat A, Safaee S. Congestion and sleep impairment in allergic rhinitis. *Curr Allergy Asthma Rep*. 2010;10(2):113-121. doi:10.1007/s11882-010-0091-5
7. Skoner DP. Complications of allergic rhinitis. *J Allergy Clin Immunol*. 2000;105(6 Pt 2):S605-9. doi:10.1067/mai.2000.106150
8. Sullivan A, Kushnir N, (Original authors: Scarupa M, Kaliner, MA). World Allergy Organization website. In-Depth Review of Allergic Rhinitis. June, 2005. Updated October 2020. Accessed January 26, 2021. <https://www.worldallergy.org/education-and-programs/education/allergic-disease-resource-center/professionals/in-depth-review-of-allergic-rhinitis>
9. Bousquet PJ, Demoly P, Devillier P, Mesbah K, Bousquet J. Impact of allergic rhinitis symptoms on quality of life in primary care. *Int Arch Allergy Immunol*. 2013;160(4):393-400. doi:10.1159/000342991
10. Law AW, Reed SD, Sundry JS, Schulman KA. Direct costs of allergic rhinitis in the United States: estimates from the 1996 Medical Expenditure Panel Survey. *J Allergy Clin Immunol*. 2003;111(2):296-300. doi:10.1067/mai.2003.68
11. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol*. 2008;122(2 Suppl):S1-84. doi:10.1016/j.jaci.2008.06.003
12. Sertel S, Bergmann Z, Ratzlaff K, Baumann I, Greten HJ, Plinkert PK. Acupuncture for nasal congestion: A prospective, randomized, double-blind, placebo-controlled clinical pilot study. *Am J Rhinol Allergy*. 2009;23(6):e23–e28. doi:10.2500/ajra.2009.23.3380
13. GM Instruments website. Peak Nasal Inspiratory Flow (PNIF) Meter. Accessed December 24, 2022. <https://gm-instruments.com/products/nasal-measurements/pnif-meter>
14. Balsalobre Filho L, Pezato R, Gasparini H, Haddad F, Gregório L, Fujita R. Acute impact of continuous positive airway pressure on nasal patency. *International forum of allergy & rhinology*. 2017;7doi:10.1002/alr.21948
15. Balsalobre L, Figueiredo AB, Pezato R, Fujita RR. Effect of topical corticosteroids on nasal patency after acute positive airway pressure exposure. *Braz J Otorhinolaryngol*. 2021;87(3):326-332. doi:10.1016/j.bjorl.2019.09.011

16. Xue CC, English R, Zhang JJ, Da Costa C, Li CG. Effect of acupuncture in the treatment of seasonal allergic rhinitis: a randomized controlled clinical trial. *Am J Chin Med*. 2002;30(1):1-11. doi:10.1142/S0192415X0200020X
17. Xue CC, An X, Cheung TP, et al. Acupuncture for persistent allergic rhinitis: a randomised, sham-controlled trial. *Med J Aust*. 2007;187(6):337-341. doi:10.5694/j.1326-5377.2007.tb01275.x
18. Lumry W, Prenner B, Corren J, Wheeler W. Efficacy and safety of azelastine nasal spray at a dose of 1 spray per nostril twice daily. *Ann Allergy Asthma Immunol*. 2007;99(3):267-72. doi:10.1016/S1081-1206(10)60663-1
19. Yuan Y, Ren J, Huang L, et al. *Chinese English Dictionary of Traditional Chinese Medicine*. RenMinWeiSheng, 1997.
20. Feng S, Han M, Fan Y, et al. Acupuncture for the treatment of allergic rhinitis: a systematic review and meta-analysis. *Am J Rhinol Allergy*. 2015;29(1):57-62. doi:10.2500/ajra.2015.29.4116
21. Yin Z, Geng G, Xu G, Zhao L, Liang F. Acupuncture methods for allergic rhinitis: a systematic review and bayesian meta-analysis of randomized controlled trials. *Chin Med*. 2020;15:109. doi:10.1186/s13020-020-00389-9
22. Cheng L, Chen J, Fu Q, et al. Chinese Society of Allergy Guidelines for Diagnosis and Treatment of Allergic Rhinitis. *Allergy Asthma Immunol Res*. 2018;10(4):300-353. doi:10.4168/aair.2018.10.4.300
23. Zhang YQ. Clinical experience in acupuncture treatment of allergic rhinitis. *J Tradit Chin Med*. 2009;29(3):186-189. doi:10.1016/s0254-6272(09)60062-5
24. Petti FB, Liguori A, Ippoliti F. Study on cytokines IL-2, IL-6, IL-10 in patients of chronic allergic rhinitis treated with acupuncture. *Tradit Chin Med*. 2002;22(2):104-111.
25. Sun PL. *Management of Postoperative Pain with Acupuncture*. Elsevier Churchill Livingstone, 2007.
26. Kaliner MA. Azelastine and olopatadine in the treatment of allergic rhinitis. *Ann Allergy Asthma Immunol*. 2009;103(5):373-80. doi:10.1016/S1081-1206(10)60355-9
27. Berger WE, Fineman SM, Lieberman P, Miles RM. Double-blind trials of azelastine nasal spray monotherapy versus combination therapy with loratadine tablets and beclomethasone nasal spray in patients with seasonal allergic rhinitis. Rhinitis Study Groups. *Ann Allergy Asthma Immunol*. 1999;82(6):535-41. doi:10.1016/s1081-1206(10)63161-4
28. Horak F. Effectiveness of twice daily azelastine nasal spray in patients with seasonal allergic rhinitis. *Ther Clin Risk Manag*. 2008;4(5):1009-22. doi:10.2147/tcrm.s3229
29. Kaliner MA, Berger WE, Ratner PH, Siegel CJ. The efficacy of intranasal antihistamines in the treatment of allergic rhinitis. *Ann Allergy Asthma Immunol*. 2011;106(2 Suppl):S6-S11. doi:10.1016/j.anai.2010.08.010
30. Patel P, D'Andrea C, Sacks HJ. Onset of action of azelastine nasal spray compared with mometasone nasal spray and placebo in subjects with seasonal allergic rhinitis evaluated in an environmental exposure chamber. *Am J Rhinol*. 2007;21(4):499-503. doi:10.2500/ajr.2007.21.3058
31. Han D, Chen L, Cheng L, et al. A multicenter randomized double-blind 2-week comparison study of azelastine nasal spray 0.1% versus levocabastine nasal spray 0.05% in

- patients with moderate-to-severe allergic rhinitis. *ORL J Otorhinolaryngol Relat Spec.* 2011;73(5):260-5. doi:10.1159/000330269
32. Horak F, Ziegelmayer UP, Ziegelmayer R, et al. Azelastine nasal spray and desloratadine tablets in pollen-induced seasonal allergic rhinitis: a pharmacodynamic study of onset of action and efficacy. *Curr Med Res Opin.* 2006;22(1):151-157. doi:10.1185/030079906X80305
33. Sur DK, Scandale S. Treatment of Allergic Rhinitis. *Am Fam Physician*; 2010;81(12):1440-1446. June 15, 2010. Accessed February 28. 2021.
<https://www.aafp.org/afp/2010/0615/p1440.html>
34. Greiff L, Andersson M, Svensson C, Persson CG. Topical azelastine has a 12-hour duration of action as assessed by histamine challenge-induced exudation of alpha 2-macroglobulin into human nasal airways. *Clin Exp Allergy.* 1997;27(4):438-44.
35. McDonald JL, Cripps AW, Smith PK, Smith CA, Xue CC, Golianu B. The anti-inflammatory effects of acupuncture and their relevance to allergic rhinitis: a narrative review and proposed model. *Evid Based Complement Alternat Med.* 2013;2013:591796. doi:10.1155/2013/591796
36. Belgrade MJ, Solomon LM, Lichter EA. Effect of acupuncture on experimentally induced itch. *Acta Derm Venereol.* 1984;64(2):129-33.
37. Lundeborg T, Bondesson L, Thomas M. Effect of acupuncture on experimentally induced itch. *Br J Dermatol.* 1987;117(6):771-7. doi:10.1111/j.1365-2133.1987.tb07359.x
38. Pfab F, Hammes M, Backer M, et al. Preventive effect of acupuncture on histamine-induced itch: a blinded, randomized, placebo-controlled, crossover trial. *J Allergy Clin Immunol.* 2005;116(6):1386-8. doi:10.1016/j.jaci.2005.08.055
39. McDonald JL, Cripps AW, Smith PK. Mediators, Receptors, and Signalling Pathways in the Anti-Inflammatory and Antihyperalgesic Effects of Acupuncture. *Evid Based Complement Alternat Med.* 2015;2015:975632. doi:10.1155/2015/975632
40. Albrecht. Measurable impact of acupuncture on mucosal swelling of inferior turbinates: a prospective, randomized, controlled study. *Acta Oto-Laryngologica.* 2015;135:169-176. doi:10.3109/00016489.2014.973533
41. Lund I, Naslund J, Lundeborg T. Minimal acupuncture is not a valid placebo control in randomised controlled trials of acupuncture: a physiologist's perspective. *Chin Med.* 2009;4:1. doi:10.1186/1749-8546-4-1
42. Wang Y-R, Zhao J-P, Hao D-F. Is sham acupuncture a real placebo: Skeptical for sham acupuncture. *World Journal of Acupuncture - Moxibustion.* 2017;27(2):1-5.
doi:[https://doi.org/10.1016/S1003-5257\(17\)30110-1](https://doi.org/10.1016/S1003-5257(17)30110-1)
43. Briggs JP, Shurtleff D. Acupuncture and the Complex Connections Between the Mind and the Body. *JAMA.* 2017;317(24):2489-2490. doi:10.1001/jama.2017.7214
44. Jo JH, Hong KE, Kang WC, Choi SM, Park JE. Effect of acupuncture on nasal obstruction in patients with persistent allergic rhinitis: a randomised, controlled trial. *Journal of Korean Acupuncture and Moxibustion.* 2005;22(6):229-239.
45. Brinkhaus B, Witt CM, Jena S, Liecker B, Wegscheider K, Willich SN. Acupuncture in patients with allergic rhinitis: a pragmatic randomized trial. *Ann Allergy Asthma Immunol.* 2008;101(5):535-43. doi:10.1016/S1081-1206(10)60294-3
46. Brinkhaus B, Witt CM, Ortiz M, et al. Acupuncture in seasonal allergic rhinitis (ACUSAR)--design and protocol of a randomised controlled multi-centre trial. *Forsch Komplementmed.* 2010;17(2):95-102. doi:10.1159/000303012

47. Reinhold T, Roll S, Willich SN, Ortiz M, Witt CM, Brinkhaus B. Cost-effectiveness for acupuncture in seasonal allergic rhinitis: economic results of the ACUSAR trial. *Ann Allergy Asthma Immunol.* 2013;111(1):56-63. doi:10.1016/j.anai.2013.04.008
48. Choi SM, Park JE, Li SS, et al. A multicenter, randomized, controlled trial testing the effects of acupuncture on allergic rhinitis. *Allergy.* 2013;68(3):365-74. doi:10.1111/all.12053