The REPLACE study

Can exercise replace inhaled corticosteroid treatment in asthma?

A randomized, clinical trial

Statistical Analysis Plan for The REPLACE study

SAP version 1, 22 December 2020

Clinicaltrials.gov Trial registration identifier: NCT03290898

Date: 23 December 2020

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Trial Registration

Clinicaltrials.gov Trial registration identifier: NCT03290898

Research ethics committee registration identifier: H-17018372

Data Protection Agency registration identifier: BFH-2017-067

Protocol Version and Date

This document has been written based on information in the study protocol version 3, 2 October 2017.

Statistical Analysis Plan Version and Date

Version 1.

Date: December 22, 2020

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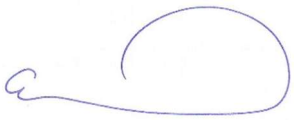
CHANGE HISTORY

Protocol Version	Updated SAP Version	Section Number Changed	Description of and Reason for Change	Date Changed

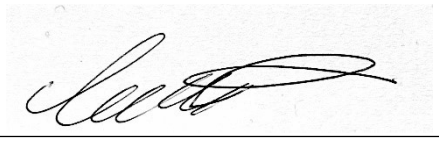
1 SIGNATURES

Approved by Study Director & Principal Investigator Vibeke Backer



Vibeke Backer, Prof, DMSci Centre for Physical Activity Research	Signature	23.12.2020 Date

Approved by Trial Manager Anders Pitzner-Fabricius



Anders Pitzner-Fabricius, MD Centre for Physical Activity Research	Signature	22.12.2020 Date

Approved by Investigator Morten Hostrup

Morten Hostrup, Associate Prof, PhD Department of Nutrition, Exercise and Sports, University of Copenhagen	Signature	22.12.2020 Date

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2 TABLE OF CONTENT

3 PURPOSE

This statistical analysis plan (SAP) describes detailed aspects of data preparation and analysis and was set up before starting the final analysis. The SAP is based on the final trial protocol (Version 3, 2 October 2017).

4 STUDY SYNOPSIS

Background and rationale:	Asthma is a highly prevalent chronic inflammatory airway disease in the western world. The cornerstone of asthma treatment is inhaled corticosteroids. However, side effects, lack of adherence to medicine and a general wish from the patients to take as low dose of medicine as possible demands us to look for non-pharmacological alternatives to treat our patients. Physical exercise as a supplementary treatment has shown to improve asthma control and life quality in patients with asthma. But it remains unknown if exercise can replace some of the daily used inhaled corticosteroids. This trial will investigate whether it is possible and safe (without development of SAE) to reduce the use of ICS when exercising for 6 months.
Objectives:	Primary objective: To assess if high-intensity interval training (HIIT) can improve asthma control to an extend that allows for a reduction in the daily use of inhaled corticosteroids. Secondary objectives: To compare the effect of HIIT vs control in changes from baseline to 6 and 12 months in: dose of ICS and LABA, lung function, airway inflammation, airway hyperresponsiveness, systemic eosinophilic inflammation, asthma-related quality of life, asthma symptoms, use of reliever medicine, body mass, fat percent, cardiopulmonary fitness, level of physical activity, exacerbations and adverse events.
Outcomes:	Primary outcome: Proportion of participants who has been reduced by at least 25% ICS at 6 months compared to baseline. Secondary outcomes: Changes from baseline to 6 and 12 months in daily dose and cumulated dose of ICS and LABA dose, FEV1, FeNO, AHR to methacholine, blood eosinophilic count, mini AQLQ, ACQ-5, use of reliever medicine, body mass, fat percent, VO_2-max, self-reported physical activity. Furthermore, safety outcomes in terms of exacerbations and adverse events are reported.
Study design:	This trial is an outcome assessor blinded, single-center, two-arm, parallel-group, 26-weeks randomized controlled trial comparing physical exercise intervention to usual lifestyle (control).
Statistical considerations:	Primary outcome will be based on an intention-to-treat principle.

For further details regarding the trial design, please see the protocol version 3, 2 October 2017.

5 INTRODUCTION

5.1 Background and Rationale

Asthma is a highly prevalent chronic inflammatory airway disease in the western world. The cornerstone of asthma treatment is inhaled corticosteroids. However, side effects, lack of adherence to medicine and a general wish from the patients to take as low dose of medicine as possible demands us to look for non-pharmacological alternatives to treat our patients. Physical exercise as a supplementary treatment has shown to improve asthma control and life quality in patients with asthma. But it remains unknown if exercise can replace some of the daily used inhaled corticosteroids. This trial will investigate whether it is possible and safe (without development of SAE) to reduce the use of ICS when exercising for 6 months.

For more details about the background, rationale and evidence base of the trial, please see the protocol version 3, 02 October 2017.

6 STUDY METHODS

6.1 Trial Design

This trial is an outcome assessor blinded, single-center, two-arm, parallel-group, 26-weeks randomized controlled trial comparing physical exercise intervention to usual lifestyle (control).

6.2 Study Objectives

The primary objective is to assess if 6 months of high-intensity interval training (HIIT) can improve asthma control to an extend that allows for a reduction in the daily use of inhaled corticosteroids.

Secondary objectives are to compare the effect of HIIT vs control in changes from base to 6 months in dose of ICS and LABA and usage of reliever medicine. Furthermore, changes in objective measurements of lung function, airway inflammation, airway hyperresponsiveness, systemic eosinophilic inflammation, body mass, fat percent and cardiopulmonary fitness are assessed.

Other secondary objectives are changes in patient-reported asthma-related quality of life, asthma symptoms and level of physical activity. Lastly, we want to evaluate on exacerbations and adverse events in the 2 groups.

6.3 Randomization

Patients will be unequal randomized 2:1 (2 to exercise: 1 to control) by a computer-based program in random block sizes, blinded to investigator. Randomization is conducted by a non-investigational member of the study group. We have a total number of strata of 8, based on the following baseline characteristics.

Stratification factors	Criterion
Sex	Female or male
Blood eosinophilic count	≥150 cells/μL
ACQ-5	> 1.75

6.4 Blinding

This is outcome assessor blinded study. Participants and trainers who delivers the intervention are not blinded. DXA scans are carried out by unblinded personnel.

Outcome assessors and study personnel performing remaining data queries and management, and the statistician will be blinded until all primary and secondary analyses are completed.

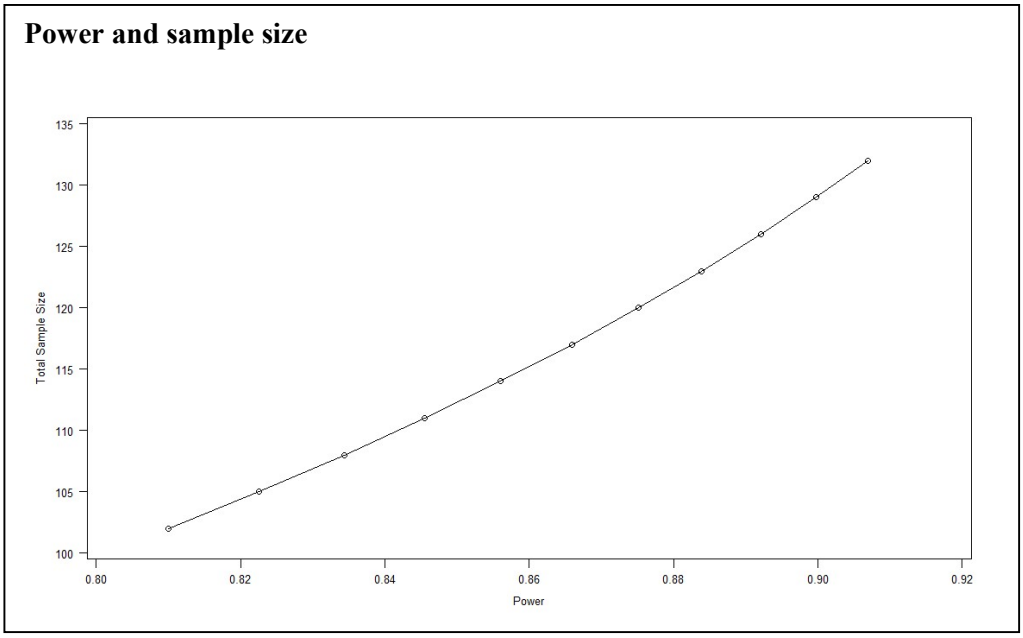
6.5 Sample Size and Power

The trial was designed as a superiority trial. We assume that at 6 months 10% in the control group (usual lifestyle) will be down-titrated by spontaneous (or via self-management) changes in ACQ score and that 35% of patients in the exercise group will be down-titrated.

For a comparison of two independent binomial proportions using Pearson's Chi-square statistic with a Chi-square approximation with a two-sided significance level of 0.05, a total sample size of 150 assuming an allocation ratio of 1 to 2 has an approximate power of 0.941 when the proportions are 0.1 and 0.35. This corresponds to a number needed to treat (NNT) of 4 patients.

Even if NNT is 5, a sample of 150 patients (ITT) will still have sufficient power (0.82) to detect absolute difference in proportion of patients acquiring successful down-titration of 20 % (30 % in exercise group vs. 10 % in usual lifestyle).

Should we not meet the a priori sample size, even a sample size of 102 will yield sufficient power to detect a difference corresponding to an NNT of 4 patients.



6.6 Framework

This is a superiority trial

6.7 Statistical Interim Analyses and Stopping Guidance

No statistical interim has been planned and there is no guidance for stopping the trial.

6.8 Timing of Final Analysis

Final analysis will take place in one stage. The first (and main) report/publication of the trial will be prepared for the exercise/control comparison when every trial participant has completed the 12-month assessment and data for the primary and secondary outcomes have been received and cleaned (anticipated to be January 2021).

6.9 Timing of Outcome Assessments

The study consists of 7-8 visits; 2-3 pre-intervention, 3 during intervention and 2 follow-up visits.

Clinical visit schedule	Screening	Baseline	Randomization	Intervention			Follow-up	
Visit	100[a]	101a/101b[a]	102	201	202	203[b]	301	302
Time (days)	-35 to -1		-8 to -1	61 ±7	122 ±7	183± 7	274 ±7	365 ±7
Informed consent	●							
Review of inclusion and exclusion criteria	●	●						
Medical history		●						
Medication review		●						
Adjustment of asthma medicine[c]		●						
Questionnaires								
• Baseline Questions		●						
• ACQ		●		●	●	●	●	●
• Mini AQLQ		●				●		●
• Self-reported physical activity		●				●		●
ICS titration				●	●	●	●	●
Adherence								
• Foster score		●		●	●	●	●	●
• Control inhalation technique		●		●	●	●	●	●
Height and weight		●				●		●
Spirometry		●		●	●	●	●	●
Methacholine challenge[d]		(●)				(●)		
Reversibility test[d]		(●)				(●)		
FeNO		●		●	●	●	●	●
Induced sputum		●				●		
Cardiopulmonary fitness test (VO2max)		●				●		
Blood test		●				●		●
Allergy test (blood test)		●						
DEXA scan[e]		●				●		
Randomization			●					

a: If inhaled medicine dose is changed in dose at visit 101a, a 28 days run-in period is required, and a visit 101b is performed. If no run-in is required 100, 101a and 101b may be merged to one visit;
b: If subject has a moderate or severe exacerbation at visit 203, an extra visit at 7 months is required. This visit will be identical to visit 203.
c: according to adjustment algorithm;
d: Methacholine requires $FEV_1 \geq 70\%$ of predicted. If $FEV_1 < 70\%$ of predicted, reversibility test is performed instead;
e: Baseline DEXA scan is performed ±14 days from randomization.

7 OUTCOMES

7.1 Primary Outcome

- Proportion of participants who has been reduced by at least 25 % ICS at 6 months compared to baseline.

7.2 Secondary Outcomes

The following outcomes are assessed as secondary outcomes:

- Proportion of participants who has been reduced by at least 50 % ICS at 6 months compared to baseline
- Proportion of participants who has been increased by at least 25 % ICS at 6 months compared to baseline
- Change from baseline to 6 months in daily dose ICS
- Cumulated ICS dose at 6 months, expressed as mean µg/day from baseline to 6 months
- Change from baseline to 6 months in LABA dose at 6 months
- Cumulated LABA dose at 6 months, expressed as mean/day (arbitrary value) from baseline to 6 months
- Change from baseline to 6 months in use of SABA > 2/week
- Change from baseline to 6 months in fraction of exhaled nitrogen oxide
- Change from baseline to 6 months in pre-bronchodilation FEV1 in absolute mL and in percent.
- Change from baseline to 6 months in airway hyperresponsiveness to methacholine
- Change from baseline to 6 months in blood eosinophilic count in cells/mL
- Change from baseline to 6 months in VO_2-max in mL/kg/min and mL/min
- Change from baseline to 6 months in total fat percent and body mass
- Change from baseline to 6 months in symptoms measured by 5-item Asthma Control Questionnaire
- Change from baseline to 6 months in quality of life measured by mini Asthma Quality of Life Questionnaire
- Change from baseline to 6 months in self-reported physical activity at a moderate intensity in min/week
- Change from baseline to 6 months in self-reported physical activity at a vigorous intensity in min/week
- All outcomes mentioned in section 7.1, 7.2 and 7.3 (primary and secondary) at 12 months, if available.

7.3 Safety Outcomes

All safety outcomes will be presented in number of events and number of participants

- Mild asthma exacerbation requiring double doses of usual inhaler treatment at least 7 days
- Moderate asthma exacerbations requiring systemic corticosteroids for at least 3 days
- Severe asthma exacerbations requiring hospitalization and systemic corticosteroids for at least 3 days
- Life-threating asthma exacerbations requiring treatment at intensive care unit
- Number of deaths
- Pneumonia requiring antibiotic treatment
- Upper airway infections
- Muscle skeletal injuries

7.4 Definitions of Outcome Variables

7.4.1 Dose of Inhaled Corticosteroids

Dose of inhaled corticosteroids will be presented as budesonide equivalents using the estimations of comparable doses provided from GINA guidelines 2016 [1]. The table below shows an overview of the equivalent doses of ICS used in the study with examples of inhalers.

Examples of inhalers	**Pulmicort Spirocort Giona Easyhaler® (reference)**	**Symbicort, Bufomix Easyhaler®, DuoResp Spiromax**	**Flixotide®, Flutiform, Salmex, Seretide®, AirFluSal**	**Alvesco®**	**Innovair®, AeroBec (spray)**	**Asmanex**	**Relvar®***
Type of cortico-steroid	Budesonide	Budesonide	Fluticasone Propionate	Ciclesonide	Beclometasone Dipropionat	Mometasone Furoate	Fluticasone Furoate
Equivalent dose	400 µg	320 µg	250 µg	160 µg	200 µg	200 µg	92 µg

*Equivalent dose of fluticasone furoate was not well established/incorporated in the guidelines at the time of the design and dose equivalence is based on a well-educated guess.

When possible, participants are kept on the same corticosteroid (e.g. budesonide) and type of administration (DPI vs. MDI) throughout the study. Preferable the same device. However, due to local or systemic side effects or patient preference, type of delivery and steroid may be changed during the study.

Primary outcome is the proportion of participants that have been reduced by at least 25 % in their daily dose of ICS after adjustment at 6 months.

Cumulated dose of ICS expressed as a mean in µg/day is calculated by adding up the daily use of ICS from baseline until end of intervention/control (6 months) and then divide by the number of days.

Change in daily dose of ICS is the difference in the dose prescribed at baseline and the dose prescribed at 6 months visit.

An example of the two above mentioned outcomes in the same patient would be:

	61 days 0-2 months	61 days 2-4 months	60 days 4-6 month	Prescribed at 6 months	Result
Cumulated dose	400 ug	800 ug	400 ug	800 ug	(61*400+61*800+60*400)/182= 532ug
Change in dose	400 ug	800 ug	400 ug	800 ug	800 ug-400 ug= 400 ug

7.4.2 Dose of Long-Acting Beta-2-Agonists

Long-acting beta-2-agonists is added in step 5 and 6 in the study with step 6 taking double LABA dose compared to step 5. Since equivalent doses have not been established for LABAs, each treatment step is converted to an arbitrary value from 0-2;

Treatment step	1-4	5	6
Value	0	1	2

Change in daily dose of LABA is the difference in the dose prescribed at baseline and the dose prescribed at 6 months visit. Cumulated dose of LABA expressed as a mean dose (0-2) per day. Change in dose and cumulated dose is calculated as described in section 7.4.1.

Table below is an overview of which dose of LABA is prescribed at step 5 depending on prescribed inhaler.

Examples of inhalers	**Symbicort®, Bufomix Easyhaler®, DuoResp Spiromax, Oxis® Turbohaler®**	**Formo Easyhaler®, Atimos**	**Flutiform**	**Innovair®**	**Salmex Seretide® AirFluSal® Serevent®**	**Relvar®**
Type of LABA	Formoterol	Formoterol	Formoterol	Formoterol	Salmeterol	Vilanterol
Daily dose at step 5	18 µg	24 µg	20 µg	24 µg	100 µg	22 µg
Arbitrary value in analysis	1	1	1	1	1	1

7.4.3 Asthma Control Questionnaire 5-item

The 5-item Asthma Control Questionnaire (ACQ-5) is a self-administered questionnaire used to evaluate on asthma control within the last week. It consists of 5 questions regarding asthma symptoms. Each of question scores from 0-6 points, with a higher score interpreted as worse asthma control [2].

7.4.4 Mini Asthma Quality of Life Questionnaire

The short version of the Asthma Quality of Life Questionnaire (mini AQLQ) is a self-administered questionnaire used to evaluate on asthma-related quality of life within the last 14 days. It consists of 15 questions, each question falling into one of four domains: symptoms (5 items), activity limitation (4 items), emotional function (3 items) and environmental stimuli (3 items).

Each question scores from 1-7 points, with a higher score interpreted as a better asthma-related quality of life [3].

7.4.5 Pulmonary Function Test

Spirometry including test for reversibility for short-acting beta-2-agonist is performed in standing position with EasyOneTM without nasal clamp [4]. Lung function is reported as forced expiration volume in liter in 1 second (FEV1) and forced vital capacity in liter (FVC).

7.4.6 Methacholine Challenge Test

Methacholine is used to evaluate on airway hyperresponsiveness (AHR) [5]. A positive test is defined as a 20 % fall in FEV1 compared to post-diluent (saline 0,9 %) FEV1. The dose required to elicit a 20 % fall is called the PD20.The lower the dose (PD20) causing a 20 % fall in FEV1, the more severe airway hyperresponsiveness. In population where PD20 is not reached, AHR can be reported as response-dose ratio (RDR), which describes the total percentage fall in FEV1 divided by the cumulated dose of methacholine (%/µmol): $\frac{\Delta FEV \quad in\ \%}{Cumulated\ \mu mol}$. [6]

AHR will be expressed as geometrical mean of RDR ($\bar{x}_g$) in µmol based on the following equation:

$$log\ \bar{x}_g = \frac{log\ x_1 + log\ x_2 ... + log\ x_n}{n},\ \bar{x}_g = 10^{log\bar{x}_g}$$

The protocol is a modified 5-step dosimeter method suggested by the manufacturer of Jaeger/Vyntus with breath-actuated dose-release.

Provocation dose	**µmol**	**µmol cumulated**	**µg**	**µg cumulated**
PD1	0,37	0,37	72	72
PD2	0,55	0,921	108	180
PD3	0,921	1,842	180	360
PD4	1,842	3,683	360	720
PD5	3,685	7,368	720	1440

The test is conducted using SentrySuite software and Vyntus Aerosol Provocation System, a jet-nebulizer (Philips SideStream Nebulizer). Effect (N. power) is 240mg/min. Mass-median-diameter 3.2µm. Output is calculated by the equation: N.power * N. time * breaths * concentration

7.4.7 Fraction of exhaled Nitric Oxide

Fraction of exhaled nitric oxide (FeNO) was measured by a single breath test using a chemiluminescence (ECOMEDICS ANALYZER CLD 88 sp with SPIROWARE® software, gas NO-concentration was 2ppm.). Tests were carried out in accordance with ERS/ATS guidelines with a expiratory flow of 50mL/s and a minimum of two tests [7]. In case of technical issues with the device, NIOX VERO® was used.

7.4.8 Blood Eosinophilic Count

A venous blood sample was consecutively analyzed for eosinophilic count in cells/mL with 2 decimals. The test was analyzed in the central laboratory of the Hospital.

7.4.9 Specific-IgE Test

A venous blood sample was analyzed for total IgE and the following specific IgE-tests:

- House dust mites: dermatophagoides pteronyssinus (IgE-D1) and d. farinae (IgE-D2)
- Pollen: grass phleum pratense (IgE-G6), birch betula verrucosa (IgE-T3) and mugwort (IgE-W6)
- Animal epithelium: horse dander (IgE-E3), dog dander (IgE-E5) and cat dander/epithelium (IgE-E1)
- Mold: Alternaria Tenuis (IgE-M6) and Cladosporium Herbarum (IgE-M2)

The test was analyzed in the central laboratory of the Hospital. Detection limit of the assay was 0.35kUA/L.

Specific IgE-test is interpreted as either positive ($\geq$ 0.35kUA/L) or negative (< 0.35kUA/L)

7.4.10 Cardiopulmonary Fitness

VO_2-max test was performed on an ergometer cycle (Vyaire – JAEGER Oxycon Pro & Vyntus CPX). The protocol consisted of 3 minutes rest, 3 minutes unloaded warm-up, 8-12 minutes incremental phase (ramp) and a recovery period of a minimum of 1 minute. The criteria for passing the test were a respiratory exchange ratio ≥1.05 [8]. Changes in aerobic fitness will be presented in absolute (mL/min) and relative (mL/kg/min) values.

7.4.11 Self-Reported Physical Activity

Self-reported physical activity was reported as average time (minutes) spent per week within the last 2 months. Activities were divided into moderate intensity (3.0-6.0 METS) and vigorous intensity (> 6.00 METS). Participants was given examples of types of exercise within each intensity group before reporting their activity level.

7.4.12 Body composition

Body composition is measured with dual-energy x-ray absorptiometry (Norland DXA, model XR-800, software Illuminatus 4.7.4, software version: 2.3.1) pre- and post-intervention. Change in total fat percent (%) is calculated as difference between pre- and post-intervention divided by pre-intervention value

$$\frac{Fat\ percent_{\ post\ \_\ intervention}\ (\%)\ - fat\ percent_{pre\ \_\ intervention}\ (\%)}{fat\ percent_{\ pre\ \_\ intervention}(\%)} \times 100\ \%$$

7.5 Adverse and Serious Adverse Events

The investigators and clinical staff monitor each participant for evidence of adverse events (AEs) and serious adverse events (SAEs) throughout the study. The investigator will assess and record any AE and SAE in detail including the date of onset, description, severity, duration and outcome, relationship to study treatment, and any action(s) taken.

An investigator will adjudicate all reported AEs and SAEs based on available and relevant medical records.

8 DATA MANAGEMENT

8.1 Data Validation

All variables used in the database, including derived variables, will be checked for missing values, outliers and inconsistencies. We do not expect many faulty data points because error checks and warnings were implemented into the eCRF and database system.

8.2 Data Preparation

8.2.1 Changes from Baseline

OUTCOME	INTERPRETATION OF POSITIVE CHANGE
ACQ-5	Worsening
Mini-AQLQ	Improvement
AHR to methacholine, DRS	Worsening
FEV1	Improvement
FVC	Improvement
FeNO	Worsening
VO2max	Improvement
Blood eosinophilic cell count	Worsening

9 TRIAL POPULATIONS

9.1 In- and Exclusion Criteria

Inclusion criteria

- Asthma
- 18-75 years
- ACQ ≥ 1 and ≤ 2.5
- On a daily dose of ICS at a minimum of 400 µg budesonide or equivalent ICS for 3 months and with no changes in asthma medicine 4 weeks prior to enrolment
- Untrained (no participation in vigorous exercise for more than 1 hour per week during the last 2 month)
- Capable of exercising on bike

Exclusion criteria

- Unable to speak and understand Danish
- Infection in the respiratory tract within 4 weeks prior to visit 100*
- Asthma exacerbation within 4 weeks prior to visit 100*
- Hospitalized for an asthma attack during the last 2 months.
- Treatment with immunotherapy within 5 T½ of the treatment drug prior to visit 100
- Initiation of allergen immunotherapy within 3 months prior to visit 100 or plan to begin therapy during study period.
- Treatment with peroral prednisolone
- Respiratory: other chronic pulmonary disease of clinically significance
- Cardiovascular: Unstable ischemic heart disease, myocardial infarction within the last 12 months, symptomatic heart failure (NYHA III-IV or EF < 40%), symptomatic heart arrhythmia (documented with ECG), uncontrolled hypertension (> 155/100)
- Pregnancy or breastfeeding or planned pregnancy within the next 12 months.
- Other inflammatory or metabolic diseases with the exception of rhinitis, atopy and well-controlled hypothyroidism treated with or without Eltroxin.

- Vaccination less than 2 weeks prior to any visit requiring blood samples
- Current or former smokers with > 20 pack years
- Subjects, who by investigators determination, will not be able to adhere to study protocol

*If patients are excluded due to a recent infection or exacerbation, they can undergo re-screening after a total of 4 weeks after end of exacerbation treatment/clearing the infection.

9.2 Participant Flow

A CONSORT participant flow diagram will be drawn following the CONSORT standards (see Shell Figure 1).

The flow diagram will be used to summarize the number of patients who were:

- assessed for eligibility
- not eligible
- not interested in participating after screening
- eligible and randomized
- allocated to each intervention
- received the randomly allocated intervention
- discontinued the intervention*
- lost to follow-up at month 2, 4, 6, 9 and 12*
- randomized and included in the primary analysis (intention-to-treat population)

*reasons will be provided.

9.3 Intention-To-Treat Population

The Intention-To-Treat (ITT) population consists of all randomized patients irrespective of whether the patient actually received study intervention or the patient's compliance with the study protocol, in the group (exercise/control) to which the participant was assigned to at randomization. A patient will be considered randomized as soon as treatment is assigned according to allocation sequence (i.e. breaking the allocation concealment for an enrolled individual).

The participant demographics and baseline data for the ITT population will be summarized in a table (shell Table 2). Participants will be described with respect to baseline age, sex, height, body mass, body mass index, smoking status, specific IgE, treatment step, inhaler technique, stratification factors and baseline values of primary, secondary and safety, separately for the two groups.

Continuous data will be summarized by means and SDs. Categorical data will be summarized by numbers and percentages. Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted.

9.4. Safety Population

Safety population consists of the participants randomized for exercise who have received intervention at least one time and the full control group.

9.5 Adherence to Exercise

At each session of HIIT a trainer would register all attendants. Every second week participants attendance would be checked by an unblinded member of the study team. If the participant had missed > 1/3 of the planned session (3/week) the study member would contact the participant to encourage him/her to attend HIIT sessions and clarify if there were any problems regarding exercise (injury, lack of time, lack of commitment etc.) that needed to be addressed. If training is stopped due to safety, adherence will be determined by the attendance prior to stop in training.

9.6 Adherence to Medicine

Adherence to medicine will be evaluated by Foster score. The score ranges from 0/7 to 7/7, meaning that that the patient has taken the prescribed dose 0 days out of 7 days the last 7 days and 7 days out of 7 days the last 7 days, respectively. If the patient had misunderstood the prescribed dose, e.g. thought he/she should take 1 puff once-a-day but was prescribed 1 puff twice-a-day, adherence was evaluated on the basis of the patients belief, in this case 1 puff once-a-day. Furthermore, patients were asked if they ever forgot to take their medicine. If answered with “yes”, they were asked how frequent they forgot (daily, weekly, monthly, annually) and adherence was evaluated by a cut-off point at 80% (≥80%).

If a patient in between two visits is taken another dose of medicine than prescribed, then medicine was adjusted according to 2 factors at next visit:

1) ACQ-5 score (low, intermediate or high), and
2) Intention, was the change in medicine intentionally (e.g. poor asthma control and need for a higher daily dose that couldn't be handled as an exacerbation; or good asthma control where the patient felt he/she needed to reduce treatment)

Dose taken	Intentionally	ACQ-5 ≤1.0	ACQ-5 >1.0-1.5	ACQ-5 > 1.5
Higher	Yes (bad control)	No change	No change	No change
	No (misunderstanding)	⬇ 1 step down	No change	No change
Lower	Yes (good control)	No change	No change	⬆ 1 step up
	No (misunderstanding)	No change	No change	⬆ 1 step up

10 STATISTICAL ANALYSES

10.1 General considerations

In the primary analysis, all participants will be analyzed using the ITT population according to the intention-to-treat principle. All 95 % confidence intervals will be two sided.

10.2 Multiple comparisons

Due to the exploratory nature of this study, the analyses of the secondary outcomes will focus on estimation rather than inferential testing and are provided to support the clinical interpretation of the primary outcome. Thus, the analyses will not be adjusted for multiple comparisons.

Any serendipitous findings coming from exploratory analyses of the other secondary outcomes will be carefully reviewed for plausibility and it will be clearly stated that the findings may have occurred by chance.

10.3 Equivalence Margins

When reducing ICS and/or LABA the following changes would be expected in:

	Expected change when reducing ICS and/or LABA	Interpretation in terms of asthma control
FeNO	Increase in ppb	Worse
FEV1	Reduction in volume	Worse
ACQ-5	Increase in score	Worse
Mini AQLQ	Decrease in score	Worse
Methacholine challenge test	Increase in responsiveness	Worse
Blood eosinophilic count	Increase in cell counts	Worse
Use of SABA	Increase use	Worse

However, the underlying hypothesis is that the exercise intervention will have the opposite effect, wherefore it can be expected that effect of the two conditions (exercise and ICS/LABA dose reduction) may cancel each other.

However, while the primary interpretation of the secondary outcomes is based on a superiority paradigm (Exercise superior to Control) it may be necessary to interpret the results under an equivalence paradigm. Thus, the following equivalence margins are set in order to ascertain if the secondary outcomes are similar between exercise (and ICS/LABA dose reduction) and Control:

SECONDARY OUTCOMES	EQUIVALENCE MARGINS
Change in FeNO in ppb	±10ppb [9]
Change in FEV1 in L	±200mL [10]
Change in ACQ-5	±0.5 points [11]
Change in mini AQLQ	±0.5 points [12]
Change in blood eosinophilic count in cells/mL	±0.15*
Airway Hyperresponsiveness to Methacholine	±1 SD of baseline value
PN SABA >2/week, n [%]	±15 %**

*No minimal clinically important difference for change in blood eosinophilic has been established for asthma endpoints [13]. Set after discussion among the investigators.

**No historical data or studies to inform choice of margins. Set after discussion among the investigators.

10.4 Primary Analysis

The primary analyses will be conducted according to the ITT principle. The ITT principle asserts the effect of a treatment policy (that is, the planned treatment regimen), rather than the actual treatment given (i.e., it is independent of treatment adherence). Accordingly, participants allocated to a treatment group will be

followed up, assessed and analyzed as members of that group, irrespective of their adherence to the planned course of treatment (i.e., independent of withdrawals and cross-over phenomena).

10.4.1 Primary Analysis of Primary Outcome

The primary outcome analysis will be a *superiority analysis* based on the ITT population, asking whether the Exercise is better than Control regarding the number of participants who have had their ICS dosage reduced by at least 25% from baseline at the end of the treatment period (6 months). We will use a logistic regression analysis model adjusted for stratification factors and the treatment step at baseline.

$$ICSREDUCED_{6months} \approx GROUP + Stratification_i + TREATMENTSTEP_{baseline}$$

The model will only include data from baseline and the 6 months assessment. For ease of interpretation the corresponding Odds Ratio will be converted back into Adjusted Risk Ratio and/or Risk Difference based on the number of responders in the Control group [14]. From this model the observed differences in the risk of being reduced in ICS dosage by at least 25% between Exercise and Control at month 6 will be estimated together with the associated 95% confidence interval (and the p-value) corresponding to the test of the hypothesis of no difference between treatments.

Superiority will potentially be claimed if the computed 95% confidence interval of the estimated Odds Ratio (and corresponding Risk Difference) at month 6 exclude 1 (0 for the Risk Difference).

10.4.2 Primary Analysis of Secondary, Safety and Exploratory Outcomes

The primary analysis of secondary and safety outcomes will be *superiority analyses* using the ITT population.

Analyses of continuous outcomes will include all collected data, and effects will be estimated at month 6 and 12; asking whether the Exercise is superior to Control at the 6- and 12-months assessments. We will use repeated measures linear mixed model regression analyses adjusted for stratification factors and the respective baseline scores. An interaction for time and group will be included.

$$VARIABLE_{change\_month6} \approx GROUP + MONTH + GROUP \times MONTH + Stratification_i + VARIABLE_{baseline}$$

We will compute group differences with two-sided 95% confidence intervals interpreted based on the superiority paradigm.

Dichotomous outcomes will be analyzed identically to the primary outcome and adjusted for the stratification factors and the respective baseline value if available.

10.4.3 Missing Data

For the primary analyses of dichotomous outcomes (including the primary outcome) we will use a fixed-set multiple imputation framework for missing dichotomous outcomes [15]. For these binary outcome, we will a use a methodology that imputes the extreme displays that reveal the effects of all outcomes for each randomized individual, using combinations of the values of missing data in the first arm (HIIT group) and the second arm (Control group); the imputation technique is based on the idea of 'tipping-point' (TP) analysis [16]. We enhance this idea by formalizing the process of robust estimation using a more detailed display in conjunction with multiple imputation (MI) of missing data. We will semi-automatically generate **5** individual data sets based on the following approach:

Data as observed (including missing data)

- Worst ($Y_{Mis} = 0$) *AND* Worst ($Y_{Mis} = 0$) case imputation in each group, respectively
- Best ($Y_{Mis} = 1$) *AND* Best ($Y_{Mis} = 1$) case imputation in each group, respectively
- Worst ($Y_{Mis} = 0$) *AND* Best ($Y_{Mis} = 1$) case imputation in each group, respectively
- Best ($Y_{Mis} = 1$) *AND* Worst ($Y_{Mis} = 0$) case imputation in each group, respectively.

From these 4 simulated (complete) data sets as well as the original data set (with missing data), 5 different sets of the point and variance estimates will be computed. Using Rubin's rules, which take account of the variability in results between the imputed datasets, reflecting the uncertainty associated with the missing values, we will combine these results and generate valid and robust statistical inference about the multiply imputed Odds Ratio, as well as the proportions responding in each group [17].

For the primary analyses of continuous outcomes, missing data will be handled indirectly by statistically using Mixed Linear models based on the repeated-measurements framework. These models are generally considered valid if data are '*Missing at Random*' (MAR); i.e. where "*Any systematic difference between the missing values and the observed values can be explained by differences in observed data*" (4). Contrasts between groups will be estimated based on repeated-measures mixed linear models across all timepoints (i.e., with explicit estimates derived at 6 and 12 months from baseline, respectively).

10.5 Missing Data due to COVID-19 Pandemic

Lockdown was established in Denmark from March 13th, 2020. When lockdown was instituted 15 patients (10 %) were still receiving exercise intervention/control. Exercise classes were cancelled and participants receiving exercise intervention were instructed to continue training at home.

Partial reopening was slowly initiated from April 15th, 2020. During complete lockdown and the initial period of reopening 2-, 4- and 9-month visits (V201, v202 and v301) were carried out as telephone visits, leading to missing data with regards to lung function, FeNO and check of inhalation technique at these visits.

6- and 12-month (V203 and V302) visits were kept as physical visits. Induced sputum was considered high-risk procedure with respect to SARS-CoV-2 and were not carried out in the last 15 participants.

In patients with high risk of a severe *course* of SARS-CoV-2 infection, 6- and 12-month visits (V203 and v302) were postponed at the participant and investigator discretion. This could influence the timeline of these participants.

During lockdown and the initial part of reopening (13th of March till ultimo May 2020) no VO2-max test were able to be carried out. A few patients had them carried out up to 2 weeks after ended exercise intervention/control.

The outcomes that have not been collected due to the lockdown are defined as *missing completely at random*.

We define a pre-SARS-CoV-2 population as all participants who had a scheduled primary endpoint visit (6 months visit) prior to the lockdown on March 13, 2020.

10.6 Robustness and Sensitivity Analyses

Our primary analyses will be based on the ITT population, including all randomized participants with available data at baseline.

Robustness is a concept that refers to the sensitivity of the overall conclusions to various limitations of the data, assumptions, and analytic approaches to data analysis. Robustness implies that the treatment effect and primary conclusions of the trial are not substantially affected when analyses are carried out based on alternative assumptions or analytic approaches. Therefore, we will perform sensitivity analyses for the primary and secondary outcomes.

For the primary outcome we will present the results of each of the 5 datasets defined in section 10.3.3.

For the secondary outcomes we will perform an analysis of covariance of the secondary outcomes at month 6 on the ITT population, with multiple imputation of missing data at month 6 adjusted for stratification factors and the baseline values. Each outcome variable will be imputed separately. We will use baseline variables and group allocation as predictors in the imputation models.

The imputation will be performed according to the following steps:

1. Missing values are imputed based on observed data where 5 copies of the dataset will be generated;
2. For each of the 5 copies, missing values at the month 6 visit will be analyzed using an ANCOVA model including treatment group, and stratification factors as fixed factors and the baseline level as covariates;

$$VARIABLE_{change\_week9} \approx GROUP + Stratification_i + VARIABLE_{baseline}$$

3. From these repeated standard ANCOVA models, estimated differences between groups in each of the imputed datasets will differ (at least slightly) because of the variation introduced in the imputation of the missing values, and they are only useful when averaged together to give overall estimated associations. The corresponding standard errors will be calculated using Rubin's rules, which take account of the variability in results between the imputed datasets, reflecting the uncertainty associated with the missing values [17]. Valid inferences are obtained because we will be averaging over the distribution of the missing data given the observed data.

Secondly, we will repeat the analysis of covariance of the secondary outcomes at month 6 on the ITT population, with a baseline observation carried forward imputation of missing data at month 6 adjusted for stratification factors and the baseline values

$$VARIABLE_{change\_week9} \approx GROUP + Stratification_i + VARIABLE_{baseline}$$

If the sensitivity analyses are in agreement and the sensitivity analyses and the primary analysis lead to essentially the same conclusions, confidence in the results is increased.

The result of the sensitivity analyses will be presented in supplementary tables.

10.6.1 Potential Influence of the SARS-CoV-2 Pandemic

Approximately 90 % of the participants had completed the trial when the pandemic caused a lockdown of non-critical activities in Denmark (including intervention delivery and selected outcome assessments in this trial, see section 10.5). To assess if the SARS-CoV-2 pandemic has influenced the primary results, we will analyze the pre-SARS-CoV-2 population using the primary analysis (described below). If the analyses of the pre-SARS-CoV-2 and the primary analyses are in agreement, we may claim that the study was only minimally affected by the pandemic and lockdown.

10.7 Statistical Software

The analysis will be carried out using the statistical software SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS version 25.

10.8 Harms

Analyses of AEs and SAEs will be performed on the Safety Population (see section 9.4).

The number (and percentage) of patients experiencing AEs and SAEs will be presented for each treatment arm categorized by severity. For each patient, only the maximum severity experienced of each type of AE/SAE will be displayed.

AEs and SAEs will be assessed for relationship with the trial treatment and the number (and percentage) of related AE/SAE will be presented for each treatment arm.

Deaths and AEs/SAEs leading to discontinuation of study treatment will be listed.

No formal statistical testing will be undertaken.

The AEs/SAEs will be presented in a table.

10.9 Timing of Analyses

Last patient last visit was 4th of December 2020. When this statistical analysis plan was signed outcome-assessors were still blinded and database management was not finished. We expect to close the database no later than the 15th of January 2021. Statistical analyses will start when database is closed and are expected to be completed within 2 months.

11 DEVIATIONS FROM THE PROTOCOL

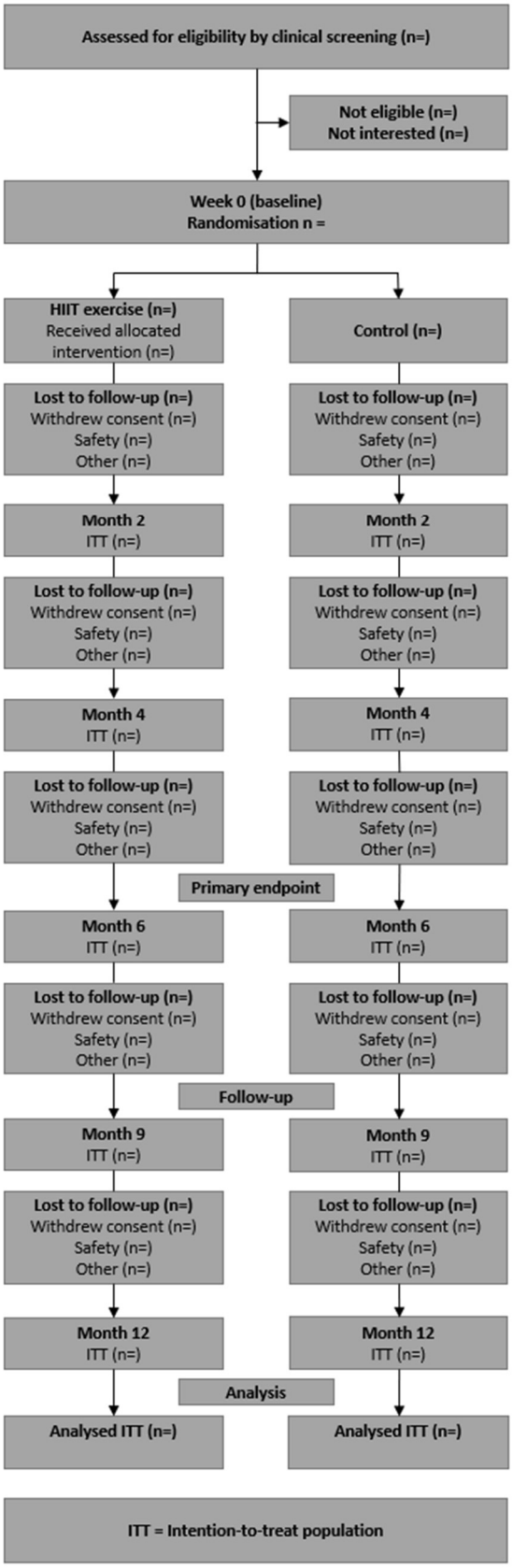
- In the protocol Methacholine challenge test is described as performed using Ad Modum Yan. This is not the case. Please see section 7.4.6 for further details regarding
- Exclusion criteria: “Hospitalized for an asthma attack during the last 12 months” was changed to “Hospitalized for an asthma attack during the last 2 months”
- Change in LABA dose in daily micrograms is changed to dummy values 0-2, please see section 7.4.2 for further details.

- In the protocol and at www.clinicaltrials.gov follow-up period (6-12 months) was planned to be open-label. However, the investigators remained blinded throughout the study to strengthen the results of the follow-up period.
- In order to evaluate on adherence to medicine, the protocol V3 October 2, 2017 included that asthma treatment was changed to a device with dose counter and the dose counter would be checked at each visit. However, this was deemed unfeasible due to the lack of dose counter in many devices. To evaluate adherence Forster score and evaluating whether the patient had taken $\geq$ 80% of prescribed dose was used. Please see section 9.6 for more details.
- Added systematically approach to handle deviations from prescribed treatment. Please see section 9.6 for further details.
- Treatment steps was renamed in the following way:

Old value	1a	1b	2	3	4	5
New value	1	2	3	4	5	6

12 MANUSCRIPT OUTLINE

12.1 Shell Figure 1 (Flow Diagram)



12.2 Shell Table 1 (Adjustment Algorithm and Treatment Steps)

Table 1 – Adjustment algorithm and treatment steps		
Interpretation	**ACQ-score**	**Treatment adjustment**
Uncontrolled	>1.5	⬆ 1 step up
Partially controlled	>1.0-1.5	No change
Well controlled	≤1.0	⬇ 1 step down
Step	**Treatment**	
6	*Budesonide 800 µg and ᵗformoterol 24µg twice a day	
5	*Budesonide 600 µg and ᵗformoterol 12µg twice a day	
4	*Budesonide 400 µg twice a day	
3	*Budesonide 200 µg twice a day	
2	*Budesonide 100 µg twice a day	
1	SABA as per required	
*Budesonide equivalent ᵗFormoterol equivalent		

Adapted from *P. Gibson et al.* [18]

12.3 Shell Table 2 (Baseline Characteristics)

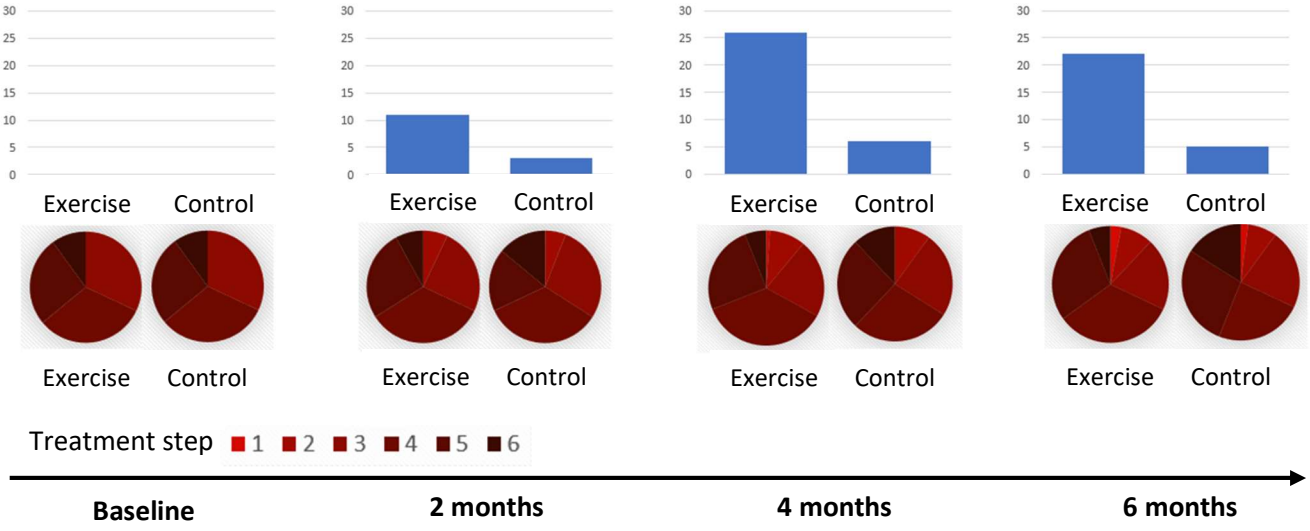
	Exercise Group	Control Group
	n=	n=
	Mean (SD)	Mean (SD)
Demographics		
Age, years	xx.x (xx.x)	xx.x (xx.x)
Body mass, kg	xx.x (xx.x)	xx.x (xx.x)
Height, m	x.xx (x.xx)	x.xx (x.xx)
Body mass index, kg/m^2	xx.x (xx.x)	xx.x (xx.x)
Current smokers, n [%]	xx (xx.x%)	xx (xx.x%)
Ex-smoker, n [%]	xx (xx.x%)	xx (xx.x%)
Pack years	xx (xx to xx)	xx (xx to xx)
Stratification factors		
Female sex, n [%]	xx (xx.x%)	xx (xx.x%)
ACQ-5 $\leq$ 1.75, n [%]	xx (xx.x%)	xx (xx.x%)
B-eosinophilic count $\geq$ 150/uL, n [%]	xx (xx.x%)	xx (xx.x%)
Exacerbations prior to inclusion		
SCS last year, number of patients [%]	xx (xx.x%)	xx (xx.x%)
Hospitalization last year, number of patients [%]	xx (xx.x%)	xx (xx.x%)
Clinical assessments		
ACQ-5 (0-6)	x.x (x.x)	x.x (x.x)
Mini AQLQ (0-7)	x.x (x.x)	x.x (x.x)
FEV1, L	x.xx (x.xx)	x.xx (x.xx)
FEV1 percent of predicted	xx% (xx.x%)	xx% (xx.x%)
FVC, L	x.xx (x.xx)	x.xx (x.xx)
FVC percent of predicted	xx% (xx.x%)	xx% (xx.x%)
FEV1/FVC-ratio	x.xx (x.xx)	x.xx (x.xx)
RDR FEV1%/µmol methacholine, geometric mean	xx.x (x.x)	xx.x (x.x)
FeNO, ppb	xx.x (x.x)	xx.x (x.x)
B-Eosinophilic, count/uL	xx (xx)	xx (xx)
Positive specific-IgE test, n [%]	xx (xx%)	xx (xx%)
Fat mass in %	xx% (xx.x%)	xx% (xx.x%)
Relative VO_2-max, mL/(kg*min)	xx (xx)	xx (xx)
Absolute VO_2-max, mL/min	xx (xx)	xx (xx)
Asthma treatment at randomization		
ICS dose in budesonide equivalents, ug/day	xx (xx)	xx (xx)
LABA score (0-2)	x.x (x.x)	x.x (x.x)
Treatment step 3, n [%]	xx (xx.x%)	xx (xx.x%)
Treatment step 4, n [%]	xx (xx.x%)	xx (xx.x%)
Treatment step 5, n [%]	xx (xx.x%)	xx (xx.x%)
Treatment step 6, n [%]	xx (xx.x%)	xx (xx.x%)
PN SABA > 2/week, n [%]	xx (xx.x%)	xx (xx.x%)
Adequate inhaler technique, n [%]	xx (xx.x%)	xx (xx.x%)
Self-reported physical activity		
Moderate intensity, min/week	xx (xx)	xx (xx)
Vigorous intensity, min/week	xx (xx)	xx (xx)

12.4 Shell Table 3 (Primary Analysis Month 6)

	Exercise group (n=)	Control (n=)	Estimated treatment difference	P-value
	n, [%]	n, [%]	OR (95% CI)	
Primary outcome:				
Proportion of participants who has been reduced by at least 25 % ICS	xx.x (xx.x%)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
	Mean (SE)	Mean (SE)	Mean (95% CI)	
Secondary outcomes:				
Proportion of participants who has been reduced by at least 50 % ICS	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Proportion of participants who has been increased by at least 25 %	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Change in ICS dose, ug/day*	xx (xx)	xx (xx)	xx (xx to xx)	
Cumulated ICS dose, ug/day*	xx (xx)	xx (xx)	xx (xx to xx)	
Change in daily dose LABA	xx (xx)	xx (xx)	xx (xx to xx)	
Cumulated LABA dose (score 0-2)	x.x (xx)	x.x (xx)	x.x (x.x to x.x)	
Change in PN SABA > 2/week, n [%]	xx (xx%)	xx (xx%)	xx (xx to xx)	
Change in FeNO, ppb	xx (xx)	xx (xx)	xx (xx to xx)	
Change in FEV1, L	xx (xx)	xx (xx)	xx (xx to xx)	
Change in FEV1, percent	xx% (xx%)	xx% (xx%)	xx% (xx% to xx%)	
Change in RDR % FEV1/µmol methacholine, geometric mean	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Change in B-eosinophilic count, cells/µL	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Change in VO_2-max, mL/kg/min	xx (xx)	xx (xx)	xx (xx to xx)	
Change in absolute VO_2-max, mL/min	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Change in body mass, kg	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Change in % fat mass	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Change in ACQ-5	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Change in mini AQLQ	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Change in moderate intensity, min/week	xx (xx)	xx (xx)	xx.x (xx.x to xx.x)	
Change in vigorous intensity, min/week	xx (xx)	xx (xx)	xx.x (xx.x to xx.x)	
	Mean (SE)	Mean (SE)	Mean (95% CI)	
Treatment adherence				
Attendance to HIIT	xx % (xx%)			
Adherence to HIIT $\geq$ 66,7 %	xx % (xx%)			
Foster score	x.x (x.x)	x.x (x.x)	x.x (x.x to x.x)	
Adherence to medicine ≥ 80 %	xx % (xx%)	xx % (xx%)		
*In budesonide equivalence				

12.5 Shell Figure 2 (As Observed Change in ICS treatment/Proportion Reduced by 25% ICS)

Number of participants in each group who has been reduced by 25 % in daily ICS treatment (bar chart) and the distribution of treatment steps (pie chart) at baseline, 2, 4 and 6 months.



12.6 Shell Table 4 (Analysis Month 12)

	Exercise group (n=)	**Control (n=)**	**Estimated treatment difference**	**P-value**
	n, [%]	n, [%]	OR (95% CI)	
Primary outcome:				
Proportion of participants who has been reduced by at least 25 % ICS	xx.x (xx.x%)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
	Mean (SE)	Mean (SE)	Mean (95% CI)	
Secondary outcomes:				
Proportion of participants who has been reduced by at least 50 % ICS	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Proportion of participants who has been increased by at least 25 %	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Change in ICS dose, ug/day*	xx (xx)	xx (xx)	xx (xx to xx)	
Cumulated ICS dose, ug/day*	xx (xx)	xx (xx)	xx (xx to xx)	
Change in daily dose LABA	xx (xx)	xx (xx)	xx (xx to xx)	
Cumulated LABA dose (score 0-2)	x.x (xx)	x.x (xx)	x.x (x.x to x.x)	
Change in PN SABA >2/week, n [%]	xx (xx%)	xx (xx%)	xx (xx to xx)	
Change in FeNO, ppb	xx (xx)	xx (xx)	xx (xx to xx)	
Change in FEV1, L	xx (xx)	xx (xx)	xx (xx to xx)	
Change in FEV1, percent	xx% (xx%)	xx% (xx%)	xx% (xx% to xx%)	
Change in B-eosinophilic count, cells/µL	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Change in body mass, kg	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Change in ACQ-5	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Change in mini AQLQ	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)	
Change in moderate intensity, min/week	xx (xx)	xx (xx)	xx.x (xx.x to xx.x)	
Change in vigorous intensity, min/week	xx (xx)	xx (xx)	xx.x (xx.x to xx.x)	
Treatment adherence				
Foster score	x.x (x.x)	x.x (x.x)	x.x (x.x to x.x)	
Adherence to medicine ≥ 80 %	xx % (xx%)	xx % (xx%)		
*In budesonide equivalence				

12.7 Shell Table 5 (Safety Outcomes at 6 Months)

Safety outcomes				
Exacerbations with increased ICS, no events	xx (xx)	xx (xx)	xx (xx to xx)	
Exacerbations with increased ICS, no patients [%]	xx (xx%)	xx (xx%)	xx (xx% to xx%)	
Exacerbations requiring systemic corticosteroids, no events	xx (xx)	xx (xx)	xx (xx to xx)	
Exacerbations requiring systemic corticosteroids, no patients [%]	xx (xx%)	xx (xx%)	xx (xx% to xx%)	
Exacerbations requiring hospitalization, no events	xx (xx)	xx (xx)	xx (xx to xx)	
Exacerbations requiring hospitalization, no patients [%]	xx (xx%)	xx (xx%)	xx (xx% to xx%)	
Death	xx (xx)	xx (xx)	xx (xx to xx)	
Pneumonia, no events	xx (xx)	xx (xx)	xx (xx to xx)	
Pneumonia, no patients [%]	xx (xx%)	xx (xx%)	xx (xx% to xx%)	
Upper airway infections, no events	xx (xx)	xx (xx)	xx (xx to xx)	
Upper airway infections, no patients [%]	xx (xx%)	xx (xx%)	xx (xx% to xx%)	
Muscle skeletal injuries, no events	xx (xx)	xx (xx)	xx (xx to xx)	
Muscle skeletal injuries, no patients [%]	xx (xx%)	xx (xx%)	xx (xx% to xx%)	

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