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A randomized, double blind study testing the effect of indacaterol on exhaled and circulatory biomarkers of COPD

The effect of Indacaterol on biomarkers of COPD

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Ethics and Good Clinical Practice

This study was planned and shall be performed according to the principles of Good Clinical Practice, the declaration of Helsinki, and national laws and regulations about clinical studies. The study may not start without written Institutional Review Board/Independent Ethics Committee/Research Ethics Board approval and the written informed consent of the patient.

# Introduction

The composition of exhaled breath provides valuable information about biochemical processes in the lung and offers new possibilities for non-invasive medical diagnosis and understanding of lung disease. Notably, exhaled breath represents an elimination pathway and can be noninvasively sampled as often as required. The technique we are using is off-line laboratory analysis. A single breath sample is collected in a steel canister and subjected to mass spectometry. Exhaled breath contains many different molecular species. Among them are small inorganic molecules such as nitric oxide (NO) and carbon monoxide (CO). Many organic volatile compounds (VOCs) have been detected in exhaled breath: the highest concentrations of VOCs in breath are observed for acetone and isoprene. Many other VOCs are observed at lower concentration levels around a few parts per billion or even in the parts per trillion range (ppb–ppt).

Some compounds, such as benzene, acetonitrile, 2-methyl furan, 2,5-dimethyl furan, furan, 1,3-cyclohexadiene, 1,3-cyclopentadiene, 2-methyl-1-butene and 1,4-pentadiene, are related to smoking toluene is detected in the breath of many people and shows increased concentrations in smokers. Also, various molecular species of exogenous origin is often observed, e.g. toluene and benzene, halogenated compounds, diesel and automotive fuels.

The identification and validation of breath volatile organic compound (VOC) biomarkers has the potential to improve the clinical diagnostic evaluation of several lung diseases. The collection of breath is clearly non-invasive, without direct risk to the patient. The technologies used to analyse breath contents have the potential to be inexpensive, point-of-care tests (i.e. tests that can be administered in the office or at the bedside). The ease with which breath can be tested allows one to study and use this form of testing for novel clinical purposes.

COPD is the commonest respiratory condition in the world. It is amongst the top 5 causes of global morbidity and mortality, with 1.2 million sufferers in Australia. COPD is described by two broad clinically based definitions. Chronic Bronchitis is defined as daily sputum production for 3 consecutive months for 2 consecutive years and is associated with airway damage and chronic mucus production. Emphysema is a pathological state involving dilatation of distal air spaces beyond the terminal bronchi. Emphysema is essentially distal lung damage, primarily due to loss of elastin. COPD can lead to dyspnoea, coughing, wheezing and systemic effects. Most individuals with COPD have comorbidities that could also explain their symptoms. It is challenging to distinguish the symptoms of COPD from those of other conditions, and to assess the level of control of COPD in an individual. A breath test that is able to diagnose and assess the activity of COPD would help to determine if COPD is the cause of a patient's presentation and assist with the management of COPD therapies.

Inflammation plays a major role in the pathogenesis of COPD. The inflammation present can produce reactive oxygen species (ROS). These ROS causes lipid peroxidation of cell membranes resulting in the production of hydrocarbons, which can be detected in the exhaled breath.

There is proof of principle that exhaled VOCs are unique in COPD. In a cohort of patients with had higher levels of ethane in their exhaled breath than the controls and those with COPD who were receiving inhaled corticosteroids. The ethane levels correlated with the FEV1. Nitric oxide and carbon monoxide levels were also elevated in COPD patients compared to controls. These did not differ between the treated and untreated COPD groups.

In a preliminary study we have demonstrated that although the sample size of both groups in this study is extremely small, the model developed shows that clear differences exist in the VOC profile of COPD patients and the control group. The COPD group exhibited less variability in replicate samples compared with the control group. This suggests that the VOC profile of COPD patients is less variable than that of the control group. Identification of the VOCs contributing to the separation of COPD and control group samples may identify a unique biomarker or series of unique biomarkers of the COPD condition.

A breath test has several advantages that can accurately diagnose or influence management decisions for lung diseases. In addition to advancing our understanding of the pathophysiology of diseases, an accurate breath biomarker could be developed into a test: 1) that can predict the risk of developing a disease, allowing preventive measures to be started; 2) that is an inexpensive screening test for at risk populations; 3) that is diagnostic and allows more expensive and invasive testing to be avoided; 4) that can prognosticate outcomes for a disease and, thus, influence treatment decisions; 5) that can determine disease activity; 6) that is capable of predicting the response to therapy; and 7) that is capable of following the response to therapy that has been started in order to guide the proper level of treatment

We will determine if we can distinguish between chronic bronchitis and emphysema as well as detect changes in VOCs following treatment with indacaterol. Indacaterol is an ultra-long-acting beta-adrenoceptor agonist developed by Novartis under the trade name Onbrez on November 30, 2009. It causes prolonged bronchodilation is used for the treatment of COPD. It is delivered as an aerosol formulation through a dry powder inhaler. A year-long, placebo-controlled trial suggests indacaterol may be more effective than twice-daily formoterol in improving FEV1. In addition to measuring exhaled VOCs in COPD we will investigate how indacaterol would influence VOCs. This will provide a valuable insight into the actions of long acting bronchodilators.

# Study objectives

The primary endpoint of the study is:

To characterize biomarkers in healthy subjects, mild and moderate COPD in blood and exhaled air.

The secondary endpoints are:

To assess the effects of indacaterol on biomarkers in exhaled air and blood.

To identify novel biomarkers present in both airway and blood.

# Investigational plan

## Overall study design

To determine Volatile Organic Compounds (VOC profiles), the breath of COPD patients and their controls needs to be analysed. The examination of the VOC profiles of these subjects will be done by principal component analysis, which will determine which, if any, VOCs are able to distinguish between COPD and controls. Sorbent tube collection device for the collection of VOC from breath of subjects, followed by thermal-desorption GC-MS with a non-polar GC column, simultaneously performing recollection followed by reanalysis using a more polar GC column (ref 1 and 2). Thermal desorption GC-MS will be able to determine alkane based biomarkers as well as other relatively non-polar volatile compounds in breath. This approach will match the technique used in the recent VOC in breath for COPD study from the Netherlands (reference 3, 4 and 5). This study uses a 5% Phenylmethylpolysiloxane GC column as the more polar GC column. An internal standard will be added to the sample post-collection for standardization of retention time and semi-quantitation. The method has been used to measure VOCs in asthma in our laboratory. All VOCs from C1 carbons to C40 carbon containing organic compounds will be analyzed.

**3.1 Research Plan**

We will measure blood and exhaled air biomarkers by using mass spectrometry. Each patient will exhale into a bag and the sample will then be attached to the mass spectrometer where gas will be sampled for volatile organic compounds (VOC). Corresponding VOCs will be measured in the blood (ref 6, 7, 8 and 9).

**3.2 Study Population**

**Number of centers & patients:** 1 centre, 200 patients in total (25 per arm), 25 never smoking healthy controls and 25 smoking controls.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Healthy controls | Healthy smoking controls | Mild COPD |  | Mod COPD |  |
|  |  |  | Bron | Emp | Bron | Emp |
| Placebo | nil |  |  |  | 25 | 25 |
| Treatment | nil |  |  |  | 25 | 25 |
| No placebo or treatment | 25 | 25 | 25 | 25 |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

Bron=chronic bronchitis, Emp=Emphysema

Inclusion criteria

1. GOLD Criteria for severity of COPD
   1. Mild – FEV1/FVC< 70%, FEV1< 80%
   2. Moderate – FEV1/FVC< 70%, FEV1 50-80%
2. COPD chronic bronchitis or Emphysema
3. Age – 50-70 years
4. Equal distribution of males and females
5. Experimental groups – Healthy controls, Healthy smokers, mild COPD (bronchitis and emphysema), moderate COPD (bronchitis and emphysema)-Indacaterol or placebo

**Exclusion criteria**

1. Present smokers
2. Severe CCF
3. Liver, renal failure
4. Diabetes
5. On immunosuppressive drugs
6. Auto-immune conditions such RA
7. Vascular disease – Scleroderma , SLE
8. Any history of asthma
9. Exacerbations in the last 6 weeks
10. Women of childbearing potential not using the contraception method(s) specified in this study (specify), as well as women who are breastfeeding
11. Known sensitivity to study drug(s) or class of study drug(s)
12. Patients with severe medical condition(s) that in the view of the investigator prohibits participation in the study (specify as required)
13. Use of any other investigational agent in the last 30 days

3.3 Treatments

Investigational therapy and reference therapy

Investigational therapy:

Indacaterol 150 µg inhalation capsules o.d., delivered via single-dose dry-powder inhaler (SDDPI)

Reference therapy:

Placebo to indacaterol 150 µg inhalation capsules o.d., delivered via single-dose dry-powder inhaler (SDDPI)

Treatment assignment, blinding and randomization

Double blind placebo. Indacaterol (active drug) 2 weeks supply for 50 patients

Placebo 2 weeks supply for 50 patients. Treatment (Indacaterol) will be commenced on day 1 post-randomization of the study and will continue for 10 days (refer to visit table below).

Randomization will be performed by the investigator, an unblinded pharmacist will dispense the study drug to ensure double blinding. The randomization code may be broken by the investigator only in a medical emergency. The reasons for this have to be documented carefully.

Concomitant therapy

Interruption or discontinuation of treatment

No adjustments to study drug dosage or schedule are permitted. In the event that the patient experiences a COPD exacerbation, the investigator should treat the patient as deemed necessary for the exacerbation.

Every patient has the right to discontinue study participation at any time, and every patient may be discontinued from the study for any reason beneficial to his/her wellbeing. All data generated up to the time of discontinuation from the study will be analyzed and the reason(s) for discontinuation will be recorded.

Treatment compliance

Patients will be asked to return all unused medication at each visit and at the end of the study and the quantity of returned medication will be documented.

3.4 Visits and assessments

Each patient will have a baseline exhaled air measurement (AEM) and bloods done. Another measurement of the same patient will be done a week later to establish reproducibility. They will then be subjected to a washout period. They would stop the following:

Inhaled steroids 14d before measurement

LAMA 7d before

LABA 2 days before. During the washout period patients would be allowed to take SABA at 2 puffs qid.

Once the washout period is complete, the patients would be tested for reproducibility for VOCs in exhaled air separated by 2 days. They would be able to use their short-acting beta2 agonists when necessary. Each patient’s symptoms would be monitored by telephone every second day. Any increase in shortness of breath, cough or sputum production would result in immediate recommencement of their usual treatment.

There are many studies that have used this washout protocol with no significant adverse effects. During trials using this washout method, no adverse outcomes were reported. In addition, the patients we are investigating have mild and moderate COPD and would tolerate the washout period. Therefore ceasing Inhaled steroids, LABAs and LAMAs for a limited period in time would not result in serious outcomes

**Summary:**

**Through the duration of the trial patients will be allowed to take SABAs**

Day-15 An exhaled air measurement (AEM) and bloods would be done before washout.

Day-14: Start washout, stop inhaled corticosteroids

Day-7: Stop LABAs

Day-2: Stop LAMAs

Day 0: Measure AEM and bloods

Day 1: Start Indacaterol or placebo

Day 10: Measure AEM and bloods

Day 11: Recommence inhaled steroids and usual treatment after 2 weeks of Indacaterol.

Day -15 Measure AEM and blood

Day -14 Stop ICS

Day -7 Stop LABAs

Day -2 Stop LAMAs

Day 0 Measure AEM and bloods

Day 1 Start Indacaterol or placebo

Day 10 Measure AEM and bloods

Day 11 –Restart inhalers

**Visit schedule:**

| Visit | 1 | 2 | 3 |
| --- | --- | --- | --- |
| Day | -15 | 0 | 10 |
| Informed Consent | X |  |  |
| Inclusion / Exclusion Criteria | X | X |  |
| **Drug dispensing** |
| Drug Accountability / Medication Check | X | X | X |
| Study drug code | X |  |  |
| Drug dispensing | X |  |  |
| Indacaterol dose administration record | X | X | X |
| Education about ceasing inhalers with written instructions | X | X | X |
| Concomitant Medications recorded | X | X | X |
| **Measurements** |
| Exhaled air collected | X | X | X |
| Bloods for experiments taken | X | X | X |
| **Safety Assessments** |
| Physical Examination | X | X | X |
| Vital Signs | X | X | X |
| Body Weight | X | X | X |
| Standard Hematology | X | X | X |
| Standard Biochemistry | X | X | X |
| Urinalysis | X |  |  |
| Adverse Events | X | X | X |
| **Other** |
| Study Completion |  |  | X |

**Laboratory tests**

Routine blood tests will be done at the pathology laboratory of the patients choice. These bloods include full blood count, urea and electrolytes, liver function tests and CRP. Exhaled VOCs will be done by the Chemcentre.

# 3.5 Safety Monitoring

## Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade *mild, moderate, severe*
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

* is fatal or life-threatening
* results in persistent or significant disability/incapacity
* constitutes a congenital anomaly/birth defect
* requires inpatient hospitalisation or prolongation of existing hospitalisation, *unless hospitalisation is for:*
* *routine treatment or monitoring of the studied indication, not associated with any deterioration in condition*
* *elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug*
* *treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission*
* *social reasons and respite care in the absence of any deterioration in the patient’s general condition*
* is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

**Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section *Serious adverse event reporting***

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalised/patient’s hospitalisation prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event e/CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the study drug can be found in the Product Information (PI). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

## Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local DS&E Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

## Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later).

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Information about all SAEs is collected and recorded on the SAE Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology (DS&E) Department. The telephone and fax number of local DS&E Department are provided below. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

**DS&E Department (Australia)**

**Phone:** 1800 814 677

**Fax:** 1800 650 493

**E-mail:** [drug\_safety.phauno@novartis.com](mailto:drug_safety.phauno@novartis.com)

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Follow-up information is sent to the local DS&E Department as above, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator’s Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported.Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

The Investigator will report Serious Suspected Adverse Reactions to the Australian Health Authority (TGA) within the required timeframe of 15 days as per regulations.

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# Data management and statistical methods

Investigators will enter the information required by the protocol into the Case Report Forms (CRFs).

Exploratory analyses will be performed using descriptive statistics. Data will be presented for the complete intent-to-treat population (all patients having taken at least one dose of study medication) as well as the per-protocol population (all patients who completed the study without major protocol deviations).

The assessment of safety will be based mainly on the frequency of adverse events, which includes all serious adverse events. Adverse events will be summarized by presenting for each treatment group the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

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