

**PRODUCT:** Iodinated Activated Charcoal + Potassium Perchlorate

**EudraCT No:** 2014-004433-10

**PROTOCOL No:** PL1401

**DATE:** December 16, 2014

**STATUS:** Finished 3.0

# **Treatment of Chronic Obstructive Pulmonary Disease (COPD) with Iodinated Activated Charcoal (IAC) and Potassium Perchlorate**

---

**Author:** Staffan Skogvall, MD, PhD

# Signature Page

## Principal Investigator

Anders Luts, MD, PhD  
Probare i Lund AB  
Lilla Fiskaregatan 10,  
SE-222 22 Lund,  
SWEDEN  
Fax + 46 46 12 55 80

Telephone: + 46 732 300 450  
Mobile: + 46 705 35 78 69

E-mail:  
[anders.luts@probare.se](mailto:anders.luts@probare.se)

---

## Sponsor

Staffan Skogvall, MD, PhD  
PharmaLundensis AB  
Medicon Village  
Scheelevägen 2  
SE-223 81 Lund  
SWEDEN

Telephone: + 46 46 13 27 78  
Mobile: + 46 703 14 86 93

E-mail:  
[staffan.skogvall@pharmalundensis.se](mailto:staffan.skogvall@pharmalundensis.se)

---

---

Signature

Date

---

Signature

Date

|  |
|--|
| <b>Senior Biostatistician</b>  |
| Anders Nordlund<br>Norma Lund AB<br>Traktorvägen 11<br>226 60 Lund<br>SWEDEN |
| Mobile: +46 733 420 408  |
| E-Mail: ano@norma-cro.com  |

## **CRO**

NORMA Lund AB

Traktorvägen 11

226 60 Lund

Sweden

## TABLE OF CONTENTS

|  |    |
|--|----|
| 1. SUMMARY.....  | 5  |
| 2. STUDY TIME TABLE.....                                 | 11 |
| 3. ABBREVIATIONS AND DEFINITION OF TERMS.....            | 12 |
| 4. INTRODUCTION.....                                     | 13 |
| 5. TRIAL OBJECTIVES AND ENDPOINTS.....                   | 25 |
| 6. TRIAL DESIGN.....                                     | 26 |
| 7. TIME LINE.....  | 29 |
| 8. VISITS.....   | 30 |
| 9. SELECTION AND WITHDRAWAL OF PATIENTS.....             | 33 |
| 10. TREATMENT.....                                       | 36 |
| 11. ASSESSMENT OF EFFICACY.....                          | 40 |
| 12. ASSESSMENT OF SAFETY.....                            | 45 |
| 13. STATISTICAL METHODS.....                             | 50 |
| 14. QUALITY CONTROL (QC) AND QUALITY ASSURANDE (QA)..... | 52 |
| 15. STOPPING RULES / DISCONTINUATION CRITERIA.....       | 53 |
| 16. ETHICS.....  | 54 |
| 17. DATA HANDLING AND RECORD KEEPING.....                | 56 |
| 18. REFERENCES.....                                      | 57 |
| 19. APPENDIX.....  | 58 |

## 1. SUMMARY

**Study code:** PL1401

**Title:** Treatment of Chronic Obstructive Pulmonary Disease (COPD) with Iodinated Activated Charcoal (IAC) and potassium perchlorate.

**Primary endpoint:** The main purpose is to study how a combination of IAC and potassium perchlorate affects lung function in patients with moderate – severe COPD.

Spirometry (FEV<sub>1</sub> baseline) tested at clinic visits at the start of study and after 8 weeks of treatment will be primary endpoint.

**Secondary endpoints:** The secondary objectives of this study aim to further describe how a combination of IAC and potassium perchlorate affects the COPD status and symptoms and to monitor the safety of the treatment. Secondary efficacy endpoints are:

**a)** Spirometry (FEV<sub>1</sub> post-bronchodilator and post-exercise, and FVC (=FEV<sub>6</sub>)] baseline, post-bronchodilator and post-exercise, tested at clinic visits at the start of study and after 8 weeks of treatment.

**b)** COPD assessment (CAT) scale at clinic visits at the start of the study and after 8 weeks of treatment.

**c)** St George's respiratory questionnaire at clinic visits at the start of the study and after 8 weeks of treatment.

**d)** 6 min walk test at clinic visits at the start of the study and after 8 weeks of treatment.

**Total sample size:** 80 Patients (40 + 40).

**Study design:** Double blind randomized placebo controlled parallel group study.

**Patient population:** 45-75 years old

Males and females

Females, >1 year post-menopausal, or surgically sterile

Smokers and ex-smokers, at least 10 pack years.

COPD according to GOLD II + III.

FEV% < 70

Post beta2-agonist FEV<sub>1</sub> 35 - 65 % of predicted value

Active symptomatic COPD with a COPD assessment test (CAT) score >10.

**Test drug and dosing:** **Active arm:** IAC 3 gram daily + potassium perchlorate 50 mg daily for 8 weeks (56 days +-4 days).

Each dose of potassium perchlorate comes in a capsule which should be taken with a glass of water just after rising from the bed in the morning.

Each dose of IAC comes in a 10 ml glass vial and should be poured in a glass of water, stirred and swallowed 15 min after the perchlorate dose.

**Placebo arm:** Placebo capsule daily + non-iodinated activated charcoal 3 gram daily should be taken similar to the active treatment for 8 weeks (56 days +-4 days).

### **Inclusion Criteria**

1. Consent to participate voluntarily.
2. Willing and able to comply with the study specific procedures.
3. Signed Informed Consent prior to any study procedure.
4. 45-75 years.
5. BMI 20-32.
6. Males and females.
7. Females >1 year post-menopausal, or surgically sterile.
8. Absolute GFR at least 60 ml/min.
9. Smokers and ex-smokers, at least 10 pack years.
10. COPD according to GOLD II + III.
11. Post beta2-agonist FEV<sub>1</sub> 35 - 65 % of predicted value.
12. FEV% < 70
13. Active symptomatic COPD at the screening visit with a COPD assessment (CAT) score >10 at that time.

### **Exclusion Criteria**

1. Previous/present hematological disease.
2. Previous/present thyroid disease including non-toxic goiter.
3. Iodine allergy.
4. Alcohol/drug abuse.

5. Severe psychiatric disease.
6. Alpha-1 antitrypsin deficiency
7. Heart infarction within 1 year of inclusion in this study.
8. Stroke/TIA within 1 year of inclusion in this study.
9. Other severe disease, according to the clinical investigator.
10. Oxygen treatment.
11. COPD exacerbation within 4 weeks prior to the study.
12. New use of per oral steroids within 4 weeks prior to the study (chronic treatment with the same dose is allowed).
13. Participation in another ongoing clinical trial or participation in drug trial the preceding 3 months.
14. Treatment with warfarin (Waran).
15. Patients with insulin treated diabetes.
16. Inflammatory bowel disease. (However, irritable bowel syndrome is allowed).
17. Severe heart disease with
  - \* anti-coagulant treatment and/or
  - \* severe coronary sclerosis, and/or
  - \* coronary stent and/or
  - \* Severe heart failure (New York Heart Association class 3 + 4).

**Procedure:**

Inclusion of the patients after the screening visit (V0) is followed by Visit 1 around 1 week later. At this visit, the patients undergo all tests planned, as described below. Thereafter, the patients will be randomized to either the treatment group (40 patients) or the placebo group (40 patients). The patients will then start their respective treatment. After 4 weeks +/- 7 days, the patients will visit the clinic and undergo laboratory tests and AE-interview, as described below. A patient can be withdrawn from the study at this point if blood values or GFR is abnormal, or if TSH or T3 are considerably changed, as described in section 9.3. After a total of 8 weeks +/- 4 days the

treatment period is concluded by clinic Visit 3 with examinations of all study parameters.

**Study parameters:**

- \* FEV<sub>1</sub> (baseline + post-bronchodilator + post-exercise) at clinic visits at the start of the study and after 8 weeks of treatment.
- \* FVC (baseline + post-bronchodilator + post-exercise) at clinic visits at the start of the study and after 8 weeks of treatment.
- \* COPD assessment (CAT) scale at clinic visits at the start of the study and after 8 weeks.
- \* St George’s respiratory questionnaire at clinic visits at the start of the study and after 8 weeks of treatment.
- \* 6 min walk test at clinic visits at the start of the study and after 8 weeks of treatment.
- \*Laboratory tests during all clinic visits:

| CLINICAL CHEMISTRY |   |    |         |     |    |      |      |               |  |
|--------------------|---|----|---------|-----|----|------|------|---------------|--|
| Na                 | K | Ca | Albumin | ALP | GT | ASAT | ALAT | GFR(absolute) |  |

| HEMATOLOGY |            |             |             |             |  |
|------------|------------|-------------|-------------|-------------|--|
| Hemoglobin | Leukocytes | Trombocytes | Neutrophils | Eosinophils |  |

|                  |
|------------------|
| Thyroid hormones |
|------------------|

|     |    |    |  |
|-----|----|----|--|
| TSH | T3 | T4 |  |
|-----|----|----|--|

**Analysis:**

The primary objective of the study is to demonstrate the effect of the lung function (change from baseline in spirometry parameter baseline FEV<sub>1</sub>).. This endpoint will be assessed using ANCOVA.

ANCOVA will also be used to analyse secondary endpoints. Distance covered during the six minute walk test will be analyzed using the Wilcoxon signed-rank test.

**Study site:**

Probare i Lund AB  
Lilla Fiskaregatan 10  
SE-222 22 Lund,  
SWEDEN  
Phone: 0732-300 450  
Fax + 46 46 12 55 80

**GCP**

The trial will be conducted in compliance with this protocol, ICH GCP and applicable requirements. The distribution, deliveries, storage and returns of the investigational medicine product will be handled according to the guideline of ICH GCP.

## 2. STUDY TIME-TABLE

The Study Calendar Timeline is as follows:

|  |                            |
|--|----------------------------|
| Statistical calculations pre-study                 | March 2014                 |
| Application to Medical Products Agency             | Oct 2014                   |
| Application to Ethics committee                    | Nov 2014                   |
| Design of CRF                                      | Dec 2014                   |
| Production of IAC and potassium perchlorate by APL | Jan-Feb 2015               |
| Study start  | March 2015                 |
| Conduct of study                                   | March 2015 –<br>March 2016 |
| Data Management                                    | April 2016                 |
| Clean File   | May 2016                   |
| Statistical Analysis of study results              | May 2016                   |
| Integrated medical/statistical final rapport       | June 2016                  |

### 3. ABBREVIATIONS AND DEFINITION OF TERMS

|                  |   |
|------------------|---|
| AE               | Adverse event                                 |
| CAT              | COPD Assessment Test                          |
| CRF              | Case Report Form                              |
| FEV <sub>1</sub> | Forced Expiratory Volume in one second        |
| GFR              | Glomerular Filtration Rate                    |
| GOLD             | Global initiative on obstructive lung disease |
| FVC              | Functional Vital Capacity                     |
| IAC              | Iodinated Activated Charcoal                  |
| ICS              | Inhaled Corticosteroids                       |
| LABA             | Long Acting Beta-2 Agonist                    |
| N/A              | Not applicable                                |
| PEF              | Peak Expiratory Flow                          |
| QoL              | Quality of Life                               |
| QoLQ             | Quality of Life Questionnaire                 |
| SABA             | Short Acting Beta-2 Agonist                   |
| SAE              | Serious Adverse Event                         |
| SAER             | Serious Adverse Event Report                  |
| SDV              | Source document verification                  |

## 4. INTRODUCTION

### 4.1 Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is a common and severe disease affecting hundreds of millions of people. It is the 3:rd most common cause of death in the world today, according to a recent WHO fact sheet (1). COPD has traditionally been attributed to cigarette smoke, although today an increasing number of non-tobacco smokers develop this disease. COPD is characterized by breathlessness, increased cough and mucous production, reduced stamina, increased risk of exacerbations (pneumonia) and abnormal rate of lung function decline (2). Effective treatments of COPD beyond a limited response to bronchodilators and interventions that reduce worsening of symptoms at exacerbations are lacking. In Sweden, more than 2 500 patients die every year as a result of severe COPD. Patients admitted to Intensive Care Unit with acute exacerbation of COPD have a median survival of only two years (3).

### 4.2 Iodinated activated charcoal as a drug

Iodinated activated charcoal (IAC) is one of many impregnated carbonaceous adsorbents which have chemicals finely distributed on their internal surface. The impregnation optimizes the existing properties of the activated charcoal giving a synergism between the chemicals and the charcoal (4). The carbon particles have a porous structure and a large inner surface amounting to 400 m<sup>2</sup>/g. The size of the pores is estimated to 0.3 – several thousands nanometers. The impregnation of the carbon with iodine leads to a synergism between the charcoal and the iodine with a strongly increased mercury binding capacity (5). Another important advantage is that the activated charcoal functions as an inert porous carrier of the active substance. This is of particular importance when using iodinated activated charcoal for medical purposes. Elemental iodine is highly reactive, and can be expected to quickly react with the gastric juice to form iodide salts, such as sodium iodide, directly after being swallowed. However, the iodine in the pores of the charcoal can be protected for some time, and remains in its active, elemental form until it reaches the small intestine.

**a).** According to a hypothesis, the elemental iodine reacts with mercury which is released in the bile. As a result, the body burden of mercury is reduced, which improves the lung function by restoring the release of an Epithelium Derived Relaxing Factor (EpDRF from Neuroepithelial Endocrine cells (NEE cells, also called Pulmonary NeuroEndocrine cells, PNEC) in the airways (6). Activated charcoal impregnated with 9 % elemental iodine was used in a previous clinical study which showed a significantly improved lung function of patients with moderate COPD.

**b).** However, at this stage it must be clear that there can be other mechanisms of action that instead are responsible for the bronchorelaxing effect by IAC. Potassium iodide has been used for treatment of asthma and COPD for more than 100 years, until more effective modern treatments became available (12). There are also modern in-vitro studies describing various potentially beneficial effects by iodide on the airways:

\* Enhancement of mucociliary activity by potassium iodide, *Melville GN et al, Respiration 1980;40(6):329-36.*

\* Enhancement of respiratory mucosal antiviral defenses by the oxidation of iodide, *Fischer AJ et al, Am J Respir Cell Mol Biol 2011;45(4):874-81.*

\* Potassium iodide inhibits neutrophilial chemotaxis, *Honma K et al, Acta Derm Venereol 1990 70(3):247-9.*

\* Iodide has also been reported to have some anti-inflammatory and anti-oxidative effect.

However, it must also be remembered that modern, double blind clinical studies have not shown any beneficial effect by iodide on the lung function of COPD patients at all (13). Regarding the mucolytic effect, a few studies have described some improvement, while others have not reported any improvement even regarding mucous.

At present it is difficult to conclusively determine the mechanism of action causing the improved lung function by IAC. However, it is important to remember that **this study has the potential to give information regarding this question.** Potassium perchlorate has been described to block

the absorption of iodide from the intestine, as well as in the thyroid gland (8). Provided that this dose of potassium perchlorate (50 mg) blocks intestinal absorption of almost all of the iodide released from the IAC so that no iodide can enter the body, but the airway function nevertheless improves, this would STRONGLY suggest that the airway relaxation is not caused by iodide affecting the lungs. If, on the other hand, the iodide absorption from the intestine is strongly blocked and the beneficial effect on the lungs disappear, this strongly suggests that the relaxing effect is mediated by iodide.

#### 4.3 Improved lung function of patients with COPD treated with iodinated activated charcoal (PL1101)

PharmaLundensis has performed a “Proof of concept” clinical study with IAC. This was a double blind randomized placebo controlled parallel group study with 40 patients with moderate COPD. In the IAC group, patients showed a statistically significant improvement of FEV<sub>1</sub> baseline by 130 ml compared to placebo, corresponding to 8.2 % improvement (p = 0.031\*). Furthermore, correlation statistics revealed that the improvement of FEV<sub>1</sub> baseline was highly significantly correlated to FEV<sub>1</sub> post-bronchodilator (p = 0.0020\*\*) and significantly correlated to FEV<sub>1</sub> post-exercise (0.033\*) values. In addition, FEV<sub>1</sub> post-bronchodilator, FVC baseline and FVC post-exercise were almost significantly improved.

The results from this study are described in greater detail in the paper “**Oral iodinated activated charcoal improves lung function in patients with COPD**” by Skogvall et al (7). This study has attracted a large interest, and the paper has, during the first 7 month after its publication, been downloaded 375 times, ~60 % from the USA. <http://www.pharmalundensis.se/download/file/200/>

In addition, the paper was of course also studied both in the paper version of the printed journal (Respiratory Medicine) and as an Abstract at PubMed. Clearly, our new ideas regarding the mechanisms causing COPD, and our new type of treatment have raised interest in many airway researches around the world.

#### 4.4 Side effects of IAC in COPD clinical study (PL1101)

In the above clinical study, no serious side effects directly related to the treatment was reported. The total number of unique adverse events (AE) was 18 in the IAC group and 12 in the placebo group. Three patients discontinued the treatment in the IAC group. This was caused by severe pharyngo-laryngitis (judged by the investigator to be unrelated to IAC), COPD exacerbation and hypothyreosis. Two patients in the placebo group discontinued the treatment, both caused by COPD exacerbation. In the IAC group, 8 patients developed abnormal thyroid values (TSH, T3 or T4) transiently during the treatment, while none developed this in the placebo group. Four of the patients with changes in the thyroid function had only a moderate increase of TSH. Another four patients also had changes in T4 levels (three had decreased values and one had increased value). In the subgroup analysis it is interesting to note that out of the six patients with especially good effect by IAC, three showed changes of the thyroid hormone levels, while the other three patients had normal thyroid values. **Thus, the improvement in lung function is not caused by a change in thyroid hormones.**

Other symptoms in the IAC group included constipation, diarrhea, joint injury, cough, pruritus and urticaria. In the placebo group, the patients reported abdominal discomfort, constipation, nausea, influenza, nasopharyngitis, distortion of the sense of taste, parosmia, COPD and urticaria.

In **Appendix 1** a complete list of reported side effects in PL1101 can be found.

In **Appendix 2** thyroid hormone values for all patients in the IAC group in PL1101 can be found.

#### 4.5 Use of IAC in CFS clinical study (PL1201)

IAC has also been tested in the clinical study **Treatment of Chronic Fatigue Syndrome (CFS) with Iodinated Activated Charcoal (IodoCarb<sup>®</sup>)**, Study Protocol PL1201. This was a double

blind placebo controlled parallel group study on 40 patients previously diagnosed with CFS. Primary endpoint was to assess the medical symptoms and every day social life problems caused by CFS by evaluation of a quality of life (QoL) assessment scale, and secondary endpoints were a) to objectively assess the efficacy of IodoCarb<sup>®</sup> to improve physical activity of the patients by a pedometer, and b) to assess if intake of IodoCarb<sup>®</sup> can reduce the patient's use (if any) of psychotropic drugs.

Evaluation of the data from the clinical study did not reveal any significant improvement of any endpoints, compared to placebo.

However, when evaluating this study, it has to be taken into account that there is a very large number of different mercury compounds. The main three groups are metallic mercury, organic mercury compounds and mercury salts. And there are several hundreds of organic compounds and several hundreds of mercury salts. The different compounds show different chemical and pharmaceutical properties, and bind with different affinity to different substances.

Therefore, in the future, we feel that clinical studies on chronic fatigue syndromes with other types of mercury binding substances would be warranted.

#### 4.6 Side effects of IAC in CFS clinical study (1201)

There were in total 88 adverse events reported in this study, 55 after IodoCarb and 33 after placebo. The total number of adverse events, counted uniquely by preferred term within patient, was 46 in the IodoCarb group and 31 in the placebo group. No serious adverse event was reported in the study.

In **Appendix 3** a complete list of reported side effects in PL1201 is reported.

In **Appendix 4** thyroid side effects in PL 1201 is listed.

#### 4.7 Transient changes of the thyroid hormones - use of potassium perchlorate

As has been described above, use of IAC for 1-2 months tended to affect thyroid hormone values of about half of the patients in both study PL1101 and PL 1201. The three patients with the largest change of thyroid hormone levels during the PL1101 study were followed up with renewed tests of the thyroid hormone levels until they had returned to normal values. Thus, the thyroid effect was reversible. The same tendency was found in study PL1201 where all patients who returned on the follow up test three months after termination of the treatment had normal pre-study levels of the thyroid hormones. Thus, the IAC effect on the thyroid gland was transient.

About half of the patients in both clinical studies that received IAC developed transient changes of the thyroid hormone levels. This suggests that some iodine is released from the IAC, enters the body and affects the thyroid gland. Clearly, this is not optimal for a COPD drug that may be used for significant amounts of time. It has, during the development of IAC, been found that it is impossible to completely prevent a small leakage of iodine from IAC. However, it may be possible to prevent the iodine from entering the body and affect the thyroid gland by use of an additional drug called potassium perchlorate. This substance is well-known to competitively inhibit the Na<sup>+</sup>/I<sup>-</sup> symporter (=iodide pump) which is responsible for absorption of iodide in the intestine (8), the thyroid (9) and the kidneys (10). 14-day studies of controlled exposure in volunteers have shown that iodide uptake by the thyroid (assessed as radioiodine uptake) can be inhibited to a considerable extent in humans without a significant change in circulating levels of thyroid hormone and TSH. A study reported a maximum inhibition of ~70 % relative to baseline in subjects who received a perchlorate dose of 0.5 mg/kg/day (11). **Thus, this very low dose of perchlorate (35 mg for a 70 kg patient) was previously found to be able to strongly inhibit iodide uptake in the thyroid gland, without significantly affecting the thyroid hormone levels.**

In the present clinical study (PL1401), a combination of IAC and a very low dose of potassium perchlorate will be used. The purpose is to clarify if the improvement of the lung function seen in the previous clinical study will be present also in patients where the iodide uptake has been reduced by perchlorate. If successful, IAC + potassium perchlorate may become a valuable treatment in COPD patients.

Furthermore, if perchlorate is effective in blocking the thyroid side effects of IAC, it may be possible in future studies to increase the IAC dose considerably. This may result in an even larger improvement of the lung function, because the IAC effect is most likely dose dependent. This would be highly useful in patients with severe COPD.

#### 4.8 Safety assessment of the combination of IAC and potassium perchlorate and Risk-Benefit assessment

A full report of Non-Clinical and Clinical Safety Data and a Safety Assessment for combined treatment with Potassium Perchlorate and Iodinated Activated Charcoal (IAC) in patients with severe Chronic Obstructive Pulmonary Disease (COPD) is attached to this application.

#### ***Known side effects***

##### **Activated charcoal**

Activated charcoal is essentially harmless in both animals and humans. As activated charcoal is excreted unchanged with the feces the possible toxic effects are restricted to the gastro-intestinal tract. No toxicity has been observed at 10-fold higher amounts of charcoal compared with the intended amounts with IodoCarb<sup>®</sup>. Some patients have reported constipation after taking charcoal. Activated charcoal may potentially absorb other drugs, thereby reducing the effect by them.

## Potassium iodide

In humans a modest increase in the iodine intake promotes temporary increases in the uptake of iodine by the thyroid gland and the formation of organic iodine, without inhibiting the capacity to release iodine in response to physiological demand. A larger excess iodine intake inhibits iodine release from the thyrotoxic thyroid or from thyroids in which iodine release has been accelerated by TSH. Still higher iodide intakes transiently decrease the production of thyroid hormones, an effect known as the acute Wolff-Chaikoff effect (Wolff et al., 1949; WHO, 1996). In normal people, this is followed by a return to normal levels of hormone synthesis, referred to as escape from the acute Wolff-Chaikoff effect, without a significant change in circulating hormone levels. An acute or chronic excess of iodide can also decrease circulating  $T_4$  and  $T_3$  levels and induce a hypothyroid state in some people who have underlying thyroid disorders. These effects are the result of a failure to escape from the acute Wolff-Chaikoff effect. Most people who experience iodine-induced hypothyroidism recover when the excess iodine intake is discontinued. No clinical abnormalities in thyroid hormone status occurred when healthy, euthyroid, adult males ( $n = 6$  or  $7$ ), who had no history of thyroid-related illness, ingested daily oral doses of 300 or 1,000 ug I/kg/day as either **iodine** ( $I_2$ ) or sodium iodide for 14 days. Based on measurements of urinary iodide excretion rates, the pretreatment iodide intakes were approximately 100 ug/day. The high dosage (1,000 ug I/kg/day) produced a small but statistically significant increase in serum TSH concentrations compared to a sodium chloride control group; the TSH concentrations in the control group did not exceed the normal range ( $<5$  mU/L) and reverted to control levels within 10 days after the **iodine** supplementation was ended. Serum  $T_4$  and  $T_3$  were not significantly different in the treatment groups, compared to the control group (**Iodine** and sodium iodide (DHHS/ATSDR, 2004).

With larger **iodine** exposure (over 10 mg/day), thyroid hormone release was decreased, usually within the first day. This effect was maximal after about 2 weeks, but with time this effect did not persist (Goldfrank's Toxicologic Emergencies, 2002). This may indicate that these effects may be transient during continues exposure to iodine. In another study, eight healthy euthyroid adults ingested approximately 32 mg iodine per day as tetraglycine hydroperiodide dissolved in juice or water, for 90 days (LeMar et al., 1995). Thyroid gland volumes increased significantly during the treatment and reverted to pretreatment volumes after the iodine dosing was discontinued. Serum

TSH concentrations increased significantly during treatment. None of the subjects developed clinical hypothyroidism.

There has also been reported other, less common, side effects by potassium iodide. These include: allergic reactions, inflammation in the salivary glands, upset stomach, nausea, vomiting, diarrhea, skin rash, fever, weakness, stomach pains, numbness, swelling of throat or neck (MedicineNet.com). There has even been reported lung oedema (*Huang TY. Ann. Allergy 1981;46(5):264-6*).

### **Potassium Perchlorate**

Excluding the effects secondary to the reduced iodide uptake in thyroids the general toxicity of potassium perchlorate is extremely low. The NOAEL for systemic toxicity was at least 30 mg/kg/day in rats and no systemic toxicity was observed in rabbits at dose levels up to 100 mg/kg/day. In addition, further long-term studies in rats including a two-generation study, carcinogenicity study and tumor promotion study indicated that oral intake of potassium and/or ammonium chloride in drinking water or mixed in diet was well tolerated up to more than 1000 mg/kg/day indicating very low toxicity in experimental animals. Studies on genotoxicity in vitro and in vivo showed that the compound is not mutagenic. Carcinogenicity studies according to modern protocols have not been performed. However, 2-year treatments at a high dose level indicate that adenomas and carcinomas may be induced in thyroid in the rat. It is considered that thyroid tumors are induced by chronic hormonal changes resulting in hyperplasia and hypertrophy and that the rat is over-predicting the risk for thyroid tumors in humans. Potassium perchlorate induced no effect on fertility, was not teratogenic and demonstrated no significant peri- or postnatal toxicity in a 2-generation study. No significant effects on neuro-behavior endpoints were observed in the rat. Exposure during pregnancy and/or lactation induced thyroid changes similar to those in adult animals demonstrating placental passage and excretion in milk.

Potassium perchlorate did promote the development of thyroid tumor in rats treated with DHPN. Investigations on immunotoxicity indicated that perchlorates at high a high dosage for 90 days potentiated delayed-type hypersensitivity (DTH). Additionally, in the LLNA assay perchlorate increased the sensitizing potential of DNCB at low dose levels and decreased the sensitizing potential at the high dose level of 42.5 mg/kg/day given for 90 days.

Perchlorates have generally been well tolerated in humans and have been given up to very high dose levels. The side effects were initially mild in the treatment of hyperthyroidosis and thyrotoxicosis. However, incidences of bone-marrow toxicity and occurrence of fatal aplastic anemia occurred in some patients treated in the dose range of 400 to 1000 mg/day. Aplastic anemia or granulocytopenia has not been reported at dose levels below 400 mg/day and has not been reported at high dose treatment for hyperthyroidism induced by amiodarone. Severe toxicity was not observed when treatment initiated at a high dose level and was then reduced to 40-120 mg/day for one year. Furthermore no hematological effects were observed in healthy volunteers at dosages of 30-35 mg/day.

### ***Possible interactions between activated charcoal and other drugs***

There may be questions regarding potential interactions between the activated charcoal and, particularly, severely ill patients who receive very important drugs. The following points should be noted:

a). The 2-hour interval between activated charcoal and other pharmaceuticals is well-established. In Sweden, Kolsuspension, oral suspension 150 mg/ml (Abigo) is registered as a drug. In the product resumé 4.5 Interactions it says that “charcoal and other drugs should be taken with at least 2 hours separation”.

However, we agree that when activated charcoal is given regularly during 2 months, there may be reason for additional caution.

b). Patients on Warfarine (Waran) treatment are excluded from the Protocol.

c). The patients should be instructed to take their ordinary drugs as far away in time from carbon as possible. If taking a drug once per day, this should be taken during midday or evening. If taking a drug twice per day, the second tablet should be taken just before going to bed, and the first 12 hours previously. If a patient normally rises at 07.00 and goes to bed at 22.00 the patients should take the tablets at 10.00 and 22.00, thereby allowing 3 hours between the carbon and the first tablet. This will be added to the Patient Information.

d). There are clearly a few diseases (in addition to the ones already excluded in the Study Protocol) that may be unsuitable to include in this clinical study, based on these considerations:

1. Patients with insulin treated diabetes.
2. Inflammatory bowel disease (however, irritable bowel syndrome is allowed).
3. Severe heart disease with
  - \* anti-coagulant treatment and/or
  - \* severe coronary sclerosis, and/or
  - \* coronary stent and/or
  - \* severe heart failure (New York Heart Association class 3 + 4).

### ***The efficacy of potassium perchlorate to inhibit absorption of iodide***

The amount of potassium chloride (50 mg/day) is very low. However, in a study (Greer MA, Goodman G, Pleus RC, Greer SE. Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. Environ Health Perspect. 2002 Sep;110(9):927-37.) it was found that 0.5 mg potassium perchlorate during 2 weeks reduced radioiodine absorption by more than 70 %. 0.5 mg/kg is equivalent to 35mg for a person of 70 kg. We chose a slightly higher dose 50 mg in order to achieve a slightly larger inhibition. Interestingly, 35 mg potassium perchlorate in 2 weeks did not cause any changes of the thyroid hormone levels, in spite of reducing the iodine uptake by more than 70 %!

**Our concentration (50 mg) is an estimate of what can be the appropriate amount. After this clinical study is completed, it will be possible to determine if the amount should be reduced, increased or stay the same.**

In summary, it is concluded that in the planned clinical trial the dose of IAC will be the one used in the first study (3 g/day) and be given during 8 weeks to patients with moderate - severe chronic obstructive pulmonary disease. Potassium perchlorate given at 50 mg/day will be added to the treatment with the aim to reduce changes in the thyroid function observed in about half of the patients in both the COPD clinical study and the CFS clinical study. It can be postulated that being a potent and competitive inhibitor of the iodide pump at different sites (intestine, thyroid,

kidneys) potassium perchlorate will prevent thyroid dysfunction due to possible release of iodide from IAC. The selected dose level of perchlorate is well below dose levels causing systemic side effects, but is within the range for reducing iodide uptake in thyroid effectively. As perchlorates are not subject to metabolism and as IAC is not absorbed from intestines in any substantial amount no interactions resulting in toxicity can be expected as a result of combining the two compounds.

It can be concluded that based upon published data in experimental animals and humans combining IAC with the dose of 50 mg of potassium perchlorate is justified from a safety point of view. However, as aplastic anemia is a rare side effect and as non-clinical investigations are poor predictors for this side effect, careful monitoring of the thyroid and bone marrow functions should be performed during the planned clinical trial. Pregnant or breast-feeding women should be excluded because treatment during pregnancy and lactation is causing thyroid changes in embryos and new-born pups and children.

## **5. TRIAL OBJECTIVES AND ENDPOINTS**

### **5.1 Primary Objective and Endpoint**

The main purpose is to study how a combination of IAC and potassium perchlorate affects lung function in patients with moderate – severe COPD.

Spirometry (FEV<sub>1</sub> baseline) tested at clinic visits at the start of study and after 8 weeks of treatment will be primary endpoint.

### **5.2 Secondary objectives and endpoints:**

The secondary objectives of this study aim to further describe how a combination of IAC and potassium perchlorate affects the COPD status and symptoms and to monitor the safety of the treatment. Secondary efficacy endpoints are:

- a)** Spirometry (FEV<sub>1</sub> post-bronchodilator and post-exercise, and FVC (=FEV<sub>6</sub>)] baseline, post-bronchodilator and post-exercise, tested at clinic visits at the start of study and after 8 weeks of treatment.
- b)** COPD assessment (CAT) scale at clinic visits at the start of the study and after 8 weeks of treatment.
- c)** St George's respiratory questionnaire at clinic visits at the start of the study and after 8 weeks of treatment.
- d)** 6 min walk test at clinic visits at the start of the study and after 8 weeks of treatment.

## 6. TRIAL DESIGN

Double blind randomized placebo controlled parallel group study with 80 patients (40 IAC + potassium perchlorate and 40 non-iodinated activated charcoal + placebo capsules).

|  | <b>Visit 0<br/>Screening</b> | <b>Visit 1<br/>Baseline</b> | <b>Visit 2<br/>Lab tests</b> | <b>Visit 3*<br/>End of Study</b> |
|--|------------------------------|-----------------------------|------------------------------|----------------------------------|
| Assessment /<br>Visit window               | ~Day -7                      | Day 1                       | Day 29 +-7                   | Day 56 +-4                       |
| Informed consent                           | √                            |                             |                              |                                  |
| Incl./Excl. criteria                       | √                            | √                           |                              |                                  |
| Demography                                 | √                            |                             |                              |                                  |
| Height & weight                            | √                            |                             |                              |                                  |
| COPD GOLD II + III                         | √                            |                             |                              |                                  |
| Medical history                            | √                            |                             |                              |                                  |
| Smoking history                            | √                            |                             |                              |                                  |
| Concomitant medication                     | √                            | √                           | √                            | √                                |
| Physical examination                       | √                            | √                           |                              | √                                |
| Vital signs                                | √                            | √                           |                              | √                                |
| ECG  | √                            | √                           |                              | √                                |
| Clinical chemistry/<br>Hematology          | √                            | √                           | √                            | √                                |
| Thyroid hormones                           | √                            | √                           | √                            | √                                |
| Blood Mercury                              |                              | √                           |                              | √                                |
| U-Iodide                                   |                              | √                           | √                            | √                                |
| alfa-1-antitrypsin<br>klassning av fenotyp | √                            |                             |                              |                                  |
| Spirometry                                 | √                            | √                           |                              | √                                |
| CAT Score                                  | √                            | √                           |                              | √                                |
| St Georges Respiratory<br>Questionnaire    |                              | √                           |                              | √                                |

|  |  |   |   |   |
|--|--|---|---|---|
| 6 min walk test                                  |  | √ |   | √ |
| Adverse Event                                    |  |   | √ | √ |
| <b>Randomization</b>                             |  | √ |   |   |
| Drug administration,<br>first dose at the clinic |  | √ |   |   |
| Deviations from<br>medication?                   |  |   |   | √ |

\* Visit 3 **must** be during the treatment period! Make appointment with patient at visit 2, and remind patient of appointment by phone ~one week before Visit 3.

Date of last dose should be established by the investigator.

**Clinical chemistry:** Na, K, Ca, Albumin, ALP, GT, ASAT, ALAT, GFR(absolute).

**Hematology:** Hemoglobin, Leukocytes, Trombocytes, Neutrophils, Eosinophils.

**Thyroid hormones:** TSH, T3, T4.

**eGFR(relative) is given from the lab and mathematically translated to absolute GFR by a computerized program.**

**Blood Mercury.**

**U-Iodide**

**Spirometry:** FEV<sub>1</sub> baseline, post-bronchodilator, post-exercise.

FVC (=FEV<sub>6</sub>)<sub>1</sub> baseline, post-bronchodilator, post-exercise.

**Reversibility test:** Administer bronchodilator (salbutamol 2.5 mg via nebulizer).

Perform spirometry after 15 minutes



## **8. VISITS**

### **8.1 Screening visit (Visit 0)**

The patient will be given information about the study procedures and must sign the informed consent form.

Eligibility to participate in the study will be checked.

At this visit the following procedures will be conducted and documented:

Inclusion/Exclusion criteria

Demographic data (date of birth, sex)

Body height and weight

Medical history, specifically allergy and asthma

Smoking status(current/former, number of pack years)

COPD GOLD stage

Concurrent disease

Concomitant medication

Physical examination including vital signs and ECG (heart rate, systolic and diastolic blood pressure)

Clinical chemistry/ hematology (please see above)

Thyroid function (TSH, T3 and T4)

alfa-1-antitrypsin klassning av fenotyp

Airway function measured by Spirometry; FEV<sub>1</sub> and FVC values (baseline, post-bronchodilator, post-bronchodilator, post-exercise).

CAT (COPD Assessment Test).

If the Patient fulfills all criteria for enrollment, an appointment for visit 1 will be booked.

## **8.2 Start of study visit (Visit 1)**

At this visit the following procedures will be conducted and documented:

Eligibility re-check

Concomitant medication

Physical examination including vital signs and ECG

Clinical chemistry/ hematology (please see above)

Thyroid function (TSH, T3 and T4)

Blood Mercury

U-Iodide

Airway function measured by Spirometry; FEV<sub>1</sub> and FVC values (baseline, post-bronchodilator, post-bronchodilator post-exercise).

CAT.

St Georges respiratory questionnaire (Appendix 5).

6 min walk test

## **RANDOMIZATION OF PATIENTS**

First dose of test substance is given at the clinic after randomization, and the patient is taught correct technique and instructed to take the medication in the morning.

## **8.3 Laboratory tests (Visit 2) (29 +-7 days)**

At this visit the following procedures will be conducted and documented:

Concomitant medication

Clinical chemistry/ hematology (please see above)

U-Iodide

Thyroid function (TSH, T3 and T4)

Adverse Event interview

Evaluation of possible withdrawal of patients according to paragraph 9.3!

#### **8.4 End of Study visit (Visit 3) (56+-4 days)**

The **Visit 3 MUST** be performed when patients are still taking test substance!

If a patient is unable to return for V3 until after day 60, he/she is excluded from the study!

The patient shall return study drug packages and any amount of unused drug, and the following procedures will be conducted and documented:

Concomitant medication

Physical examination including vital signs and ECG

Clinical chemistry/ hematology (please see above)

Thyroid function (TSH, T3 and T4)

Blood Mercury

U-Iodide

Airway function measured by Spirometry; FEV<sub>1</sub> and FVC values (baseline, post-bronchodilator, post-bronchodilator post-exercise)

CAT (COPD Assessment Test)

St Georges respiratory questionnaire

6 min walk test

Adverse Event interview

Deviation from medication?

Amount of unused drug will be calculated

## 9. SELECTION AND WITHDRAWAL OF PATIENTS

### 9.1 Inclusion Criteria

1. Consent to participate voluntarily.
2. Willing and able to comply with the study specific procedures.
3. Signed Informed Consent prior to any study procedure.
4. 45-75 years.
5. BMI 20-32.
6. Males and females.
7. Females >1 year post-menopausal, or surgically sterile.
8. Absolute GFR at least 60 ml/min.
9. Smokers and ex-smokers, at least 10 pack years.
10. COPD according to GOLD II + III.
11. Post beta2-agonist FEV<sub>1</sub> 35 - 65 % of predicted value.
12. FEV% < 70
13. Active symptomatic COPD at the screening visit with a COPD assessment (CAT) score >10 at that time.

### 9.2 Exclusion Criteria

1. Previous/present hematological disease.
2. Previous/present thyroid disease including non-toxic goiter.
3. Iodine allergy.
4. Alcohol/drug abuse.
5. Severe psychiatric disease.
6. Alpha-1 antitrypsin deficiency
7. Heart infarction within 1 year of inclusion in this study.
8. Stroke/TIA within 1 year of inclusion in this study.
9. Other severe disease, according to the clinical investigator.
10. Oxygen treatment.
11. COPD exacerbation within 4 weeks prior to the study.

12. *New* use of per oral steroids within 4 weeks prior to the study (chronic treatment with the same dose is allowed).
13. Participation in another ongoing clinical trial or participation in drug trial the preceding 3 months.
14. Treatment with warfarin (Waran).
15. Patients with insulin treated diabetes.
16. Inflammatory bowel disease (however, irritable bowel syndrome is allowed).
17. Severe heart disease with
  - \* anti-coagulant treatment and/or
  - \* severe coronary sclerosis, and/or
  - \* coronary stent and/or
  - \* Severe heart failure (New York Heart Association class 3 + 4).

### 9.3 Withdrawal of Patients

A patient should be withdrawn from the trial at any time if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient.

A patient should be withdrawn from the trial if he/she experiences an exacerbation which requires new/increased amounts of per oral steroids.

#### Visit 2:

A patient should be withdrawn if any blood value **at Visit 2** is outside the normal range.

A patient should be withdrawn if the absolute GFR **at Visit 2** is < 60 ml/min.

A patient should be withdrawn if TSH **at Visit 2** is  $\leq 0.2$  or  $> 10$ .

A patient should be withdrawn if T4 **at Visit 2** is abnormal ( <12 and >22).

**Before the patient is withdrawn, an additional blood test should be performed, to confirm any abnormal values. If this second test is also abnormal the patient is withdrawn, if it is normal the patient remains in the study.**

If a patient is withdrawn, the patient outcome should be documented and a Study Termination Report completed.

Patients discontinued will not be replaced.

Visit 3:

The **Visit 3** visit **MUST** be performed when patients are still taking test substance. If they are unable to return to Visit 3 until **after day 60**, they are **excluded** from the study!

## **10. TREATMENT**

### **10.1 Trial Product**

The IAC treatment is designed to reduce the COPD symptoms, possibly by increasing the excretion of mercury from the lungs. A small amount of potassium perchlorate is added to reduce absorption of iodine in the intestine, thyroid gland and kidneys. Iodinated Activated Charcoal (IAC) 3 gram x 1 is given in a 10 ml glass vial containing the exact amount of substances. Potassium perchlorate 50 mg x 1 is given in a capsule every morning during the treatment phase. The study medication for the 8 week study will be given to the patients at the “Start of study” visit (Visit 1).

### **10.2 Package and labeling of trial product**

IAC, potassium perchlorate and placebo will be produced by APL, Stockholm, Sweden in units. One active treatment unit consists of 3 grams of IAC in a 10 ml glass vial, and a capsule containing 50 mg potassium perchlorate. One placebo unit consists of 3 grams of non-iodinated activated charcoal in a 10 ml glass vial, and a capsule containing 50 mg placebo. The units are labelled according to a randomisation list.

A total of 40 glass vials containing either IAC powder for oral suspension and 40 potassium perchlorate capsules or placebo for IAC and capsules with placebo for potassium perchlorate will be packaged into a cardboard box, which is labelled according to the randomisation list. Each patient kit contains two cardboard boxes (2x30 units), corresponding to study medication for 8 weeks +/- 4 days.

Each vial and cardboard box will be labelled according to Annex 13 of the EudraLex Volume 4 Good Manufacturing Practice guidance. The labelling will be done by APL.

The boxes will also be labelled with labels in Swedish:

- “OBS! Förvaras mörkt vid 15-25 grader. Använd plast vid omrörning av kolsuspensionen”. (Note! Should be kept in the dark at 15-25 degrees C. Use a plastic spoon for stirring of the carbon suspension)

- ”Drick 1 glas vatten till varje perklorat kapsel som skall tas på morgonen”.(Drink 1 glass of water to the perchlorate capsule, which shall be taken during the morning just after rising from bed.

The boxes and the vials are numbered with patient number 101-180. There are two randomisation lists, one at APL and the other one will be stored at the Safety department of *Norma Lund AB*.

### **10.3 Study drug distribution at the clinics**

The Investigator will give the patients study drug in consecutive order (i.e give the IMP with number 101 to the first patient and the second patient will receive IMP with number 102 etc). The randomisation number will be noted in the medical record of the subject and in the CRF.

### **10.4 Blinding**

This study will be double-blind, meaning that neither the patient nor the Investigator will know which treatment (active or placebo) the patient will receive. Patients will be randomised to one of the two treatment arms. In order to ensure double blindness in the study, the packaging and labelling of the IP will be done at APL by persons not otherwise involved in the study. The study site will receive emergency envelopes containing individual treatment codes. The Investigator should keep the envelopes in a secure, limited access location to prevent inadvertent breaking of the blind. The double blind must be maintained throughout the study. The randomisation code must not be broken during the course of the study unless it is needed for the safety of the patients as judged by the Investigator.

In case of emergency where knowledge of the treatment group is considered necessary for treatment of a patient, the Investigator may open the emergency envelope(s) for that patient. In such a case, the Investigator must also contact the Sponsor and monitor at CRO. The date, time and reason for unblinding together with the Investigator’s signature must be recorded.

Suspected unexpected serious adverse reaction (SUSARs) will be unblinded for reporting to regulatory agencies and ethics committees. The CRO Safety (pharmacovigilance centre) will be

supplied with necessary information to break the study blind for individual patients as required for regulatory reporting purposes. However, the Investigator, Sponsor and study team will be kept blinded to treatment allocation. The information with regards to unblinding will be stored in a secure environment within the CRO Safety department and accessible only to CRO Safety staff. Unblinding of the study will occur after database lock.

### **10.5 Treatment Schedule**

IAC 3 gram daily + potassium perchlorate 50 mg daily for 8 weeks (56 days +-4 days).

Each dose of potassium perchlorate comes in a capsule which should be taken with a glass of water just after rising from the bed. **15 min** after the perchlorate capsule, the patients take IAC. Alternatively, patients so randomized take a placebo capsule.

Each dose of IAC comes in a 10 ml glass vial and should be stirred by a plastic spoon in a glass of water and swallowed at least 15 min after the perchlorate dose. Alternatively, patients so randomized take non-iodinated activated charcoal at this point.

**30 min after the IAC or placebo**, a small breakfast can be eaten. Other drugs should be taken at least **2 hours after the IAC**, to avoid drug interactions. Also, vitamins, minerals and various health food products should be taken at least 2 h after the IAC treatment to avoid interactions.

### **10.6 Concomitant Therapy and Restrictions of Diet**

The patients continue with all drugs that are taken regularly (including COPD drugs).

All concomitant medication will be recorded in the appropriate section in the CRF.

The only restriction in the use of other medication is Warfarin (Please see 10.7).

No restrictions in the diet are prescribed.

### **10.7 Prohibited Drugs**

Warfarin (Waran) is disallowed, because IAC may possibly influence the bleeding time

### **10.8 Treatment Compliance**

Returned study treatment (IAC, potassium perchlorate and placebo) will be counted after return.

The unused medication will be collected by the appointed person at the clinic.

### **10.9 Product Accountability**

An IAC, perchlorate and placebo accountability form will be filled in and returned to the sponsor (PharmaLundensis AB) according to a standard procedure.

## **11 ASSESSMENT OF EFFICACY**

Efficacy will be assessed by spirometry [FEV<sub>1</sub> and FVC (=FEV<sub>6</sub>)] baseline, post-bronchodilator and post-exercise, CAT score, St Georges respiratory questionnaire and 6 min Walk Test at the clinic according to the schedule of events in Section 8.

### **Method for spirometry**

#### **\* Equipment**

Spirometers must meet the specifications and performance criteria recommended in the ATS/ERS Standardization of Spirometry (Miller et al., 2005). We preliminary intend to use Carefusion Microlab spirometer.

#### **\* Calibration**

The spirometer should be calibrated, according to equipment requirements every morning before any spirometric measurements for the study are performed. Calibration reports should be printed and stored as source data at the site.

#### **\* Preparing the subject**

On study days when spirometry will be performed, patients should refrain from the following:

- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods and ice-cold beverages for 4 hours prior to spirometry
- Alcohol for 4 hours prior to spirometry.
- Strenuous activity for 12 hours prior to spirometry
- Smoking within at least 1 hour of testing
- Exposure of environmental smoke, dust or areas with strong odors.

Every effort should be made to assure consistent testing conditions throughout the study. A seated position with nose clips will be used to reduce risks related to dizziness or syncope.

To reduce the risk of diurnal variation on lung function, spirometry should start at approximately the same time of day at each visit (+/-2h).

#### **\* Performing spirometry**

The subjects' age, height and gender will be entered into the spirometer. It is important that the height is measured accurately at the study site. The nurse should ensure a good seal around the mouthpiece and nose clip, and confirm that the subject's posture is correct.

The results of spirometry should meet the ATS/ERS criteria for acceptability and repeatability. Acceptability criteria should be applied before repeatability is determined.

#### **\* Number of trials**

Spirometric assessment will be performed in triplicate according to ATS/ERS standards (Miller et al., 2005). If a subject is unable to perform a single acceptable maneuver after 8 attempts, testing must be discontinued.

#### **\* Acceptability**

An acceptable maneuver has the following characteristics:

- No hesitation or false start,
- A rapid start,
- No cough, especially during the first second of the maneuver,
- No glottis closure or obstruction by tongue or dentures,
- No early termination of exhalation (minimum exhalation time of 6 seconds is recommended, or no volume change for at least 1 second) or the subject cannot continue to exhale further).

#### **\* Repeatability**

The 2 largest FVC and FEV1 values from 3 acceptable maneuvers should not vary by more than 0.150 L.

**\* Recording of data**

FVC and FEV1 should be measured from a series of at least three forced expiratory curves that have an acceptable start of test and are free from artefact, such as a cough (i.e. “usable curves”). The largest FVC and the largest FEV1 should be recorded after examining the data from all of the usable curves, even if they do not come from the same curve Miller et al., 2005).

**\* Reversibility**

Reversibility evaluations should follow a modified version of the ATS/ERS recommendations. A pre-bronchodilator spirometry assessment should be performed after a wash-out period of at least:

12 hours for LAMA, LABA and SAMA.

6 hours for SABA.

The patients are allowed to continue with their regular treatment with phosphodiesterase-inhibitors (such as Daxas) and oral steroids at UNCHANGED dose.

Administer 400 microgram (4 x 100 microgram) of salbutamol following the completion of the pre-bronchodilator assessment. Post-bronchial spirometry assessment is then performed 10-15 min after administration of the salbutamol.

Reversibility is calculated as:

$100 \times (\text{FEV1 post-bronchodilator} - \text{FEV1 pre-bronchodilator}) / \text{FEV1 pre-bronchodilator}$

Following the reversibility testing assessment for post-bronchodilator FEV<sub>1</sub>, if lung function has been observed to have deteriorated after administration of salbutamol, the patient should be screen failed. Patients demonstrating a high reversibility may require further clinical evaluation by the investigator to rule out a diagnosis of asthma.

**\* Post-exercise spirometry**

**Around 15 min after the patient has performed the 6 min walk test, he should perform a new spirometry test, as described above for the pre-bronchodilator test.**

**Method for 6 min walk test**

Standardization of the 6MW test is very important in order to optimize the utilization of the test by sharply reducing the intraindividual and inter-center variability. The test is highly reproducible, with a variation coefficient near 8% for COPD patients. The instructions for its application are extremely important. An example of how patients should be instructed before performing the test is as follows: "This is a walking test that lasts 6 minutes. You are not permitted to run. The object is to walk as far as possible in 6 minutes. You will walk as fast as possible back and forth along this corridor, trying not to slow down when you turn at the end. The test lasts 6 minutes. If you have to rest you may but must resume walking as soon as you are able. Every 60 seconds we will tell you how much time has passed and how much is left to complete the test." Aspects relevant to acceptable standardization, such as the degree of incentive during the test, the length of the corridor, the number of tests a particular patient needs for assessment, and criteria for the administration of oxygen are discussed below.

*Encouragement.* The use of phrases of encouragement at regular intervals increases the distance walked. Although the reproducibility of the test is the same with or without encouragement, using it guarantees the test's high predictive value. In this way the reliability of comparison with previous tests performed by the same patient and the results obtained in other centers is assured, and equations of normality that have been obtained through tests performed with encouragement

can be utilized. Standard phrases at regular intervals--every 60 seconds--should be used, like: "you are doing well," "keep up the good work"; at the same time as the patient is informed of how much time has passed and how much is left before the test is completed.

*Length of the corridor.* The corridor should be at least 30 meters long, flat, and transit-free. The temperature should be agreeable which means the walk is normally performed indoors but it can be performed outside if the weather is appropriate.

*Monitoring.* Before the test starts, and with the patient stationary at one end of the corridor, heart rate, oxyhemoglobin saturation (by pulse oximetry) and perception of dyspnea (mod Borg scale), are recorded. The same variables are taken at the end of the test. The number of times the patient stops is also recorded. Finally, the distance walked in 6 minutes is recorded in meters. The distance is the primary measurement in the test.

## 12. ASSESSMENT OF SAFETY

### 12.1 Adverse Events

#### *Definition*

An **adverse event (AE)** is any untoward medical occurrence in a patient or subject administered a drug or biologic (medicinal product) or using a medical device; the event does not necessarily have a causal relationship with that treatment or usage.

Adverse events include the following:

- a. All suspected adverse reactions.
- b. All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.
- c. Apparently unrelated illnesses, including the worsening of a preexisting illness (see Preexisting Conditions, below).
- d. Injury or accidents. **Note** that if a medical condition is known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as two separate adverse events. The outcome of the accident (e.g., hip fracture secondary to the fall) should be recorded under Comments.
- e. Abnormalities in physiological testing or physical examination (findings that require clinical intervention or further investigation beyond ordering a repeat [confirmatory] test).
- f. Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (e.g., elevated liver enzymes in a patient with jaundice) should be described under Comments on the report of the clinical event rather than listed as a separate adverse event.
- g. All abnormal thyroid values (TSH, T4, T3) will be recorded as an AE.

#### *Preexisting Conditions*

In this trial, a preexisting condition (i.e., a disorder present before the adverse event reporting period started and noted on the pretreatment medical history/physical examination form) should

not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period.

### *Procedures*

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy noted under Comments.

### **12.2 Adverse Event Reporting Period**

The adverse event-reporting period for this trial begins upon starting the use of the IAC (Visit 1) and ends at the final (Visit 3) clinic visit.

All adverse events that occur in trial patients during the adverse event reporting period specified in the protocol must be reported to PharmaLundensis AB or its appointed CRO, WHETHER OR NOT THE EVENT IS CONSIDERED PRODUCT RELATED.

IN ADDITION, any known untoward event that occurs subsequent to the adverse event-reporting period that the investigator assesses as possibly related to the investigational medication/product should also be reported as an adverse event.

### **12.3 Seriousness (Gravity)**

Each adverse event is to be classified by the investigator as SERIOUS or NONSERIOUS. This classification of the gravity of the event determines the reporting procedures to be followed.

An adverse event that meets one or more of the following criteria/outcomes is classified as serious:

- Death
- Life-threatening (i.e., immediate risk of death)
- In-patient clinicization or prolongation of existing clinicization
- Persistent or significant disability/incapacity
- A congenital abnormality or birth defect
- An important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

#### **12.4 Other Medical/Scientific Judgment**

Medical judgment should be exercised in deciding whether a reaction is serious in other situations. Important adverse reactions that are not immediately life threatening or do not result in death or clinicization but may jeopardize the patient should be considered serious.

#### **12.5 Eliciting Adverse Event Information**

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial Patient. In addition, each trial Patient will be questioned about adverse events for each visit. The question asked will be “Have you notice any changes in your health since we asked last?”

#### **12.6 Reporting**

If a SERIOUS adverse event occurs, Trial Form Support (TFS) Drug Safety is to be notified, using the SERIOUS ADVERSE EVENT REPORT (SAER) form, within 24 hours of awareness of the event by the investigator. The initial report is to be followed by submission of more detailed adverse event information on the SAER form within 5 working days of the event. TFS Drug Safety will inform Norma Lund AB throughout the process.

If unexpected and related, serious adverse events (SUSARs) are also to be reported immediately (within 7 or 15 calendar days) to the Independent Ethics Committee and to the Swedish Medical

Products agency. The SAE reporting procedures are detailed in a study specific Serious Adverse event Reporting Plan. This plan is an agreement between the sponsor, the CRO Norma Lund AB and TFS Drug Safety. TFS Drug Safety has been appointed as Norma’s regulatory contact and will be responsible for the timely submission of reportable events to the regulatory authorities and Ethics Committee in accordance with ICG Good Clinical Practice and regulatory requirements. TFS Drug Safety will be responsible for reporting of SUSARs to the competent authority through the EudraVigilane Clinical Trials Modules and to the Ethics Committee.

Serious adverse events should also be reported on the clinical trial adverse event case report form.

Note: The SAER form is not the same as the adverse event case report form, however, where the same data is collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms.

NON-SERIOUS adverse events are to be reported on the adverse event case report forms, which are to be submitted to Norma Lund AB as specified in the adverse event report submission procedure for this protocol.

#### REPORTING REQUIREMENTS FOR ADVERSE EVENTS

| Gravity    | Reporting Time                            | Type of Report                |
|------------|---|-------------------------------|
| SERIOUS    | Within 24 hours                           | Initial report on SAER        |
|            | Within 5 working days                     | Final report on SAER          |
| NONSERIOUS | Per case report form submission procedure | Appropriate case report forms |

**NOTE:** In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (for example, if an outpatient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document his/her first awareness of the adverse event.

## 12.7 Recording Instructions

Adverse events are to be recorded in the case report forms as specified.

If required on the adverse event case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event.

For purposes of consistency, these intensity grades are defined as follows:

|          |   |
|----------|---|
| MILD     | Does not interfere with patient's usual function        |
| MODERATE | Interferes to some extent with patient's usual function |
| SEVERE   | Interferes significantly with patient's usual function  |

Note the distinction between the gravity and the intensity of an adverse event. **Severe** is a measure of intensity; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

The investigator will also be asked to assess the possible relationship (related/unrelated) between the adverse event and the investigational medication as well as any concomitant medications.

## 12.8 Follow-Up of Adverse Events

All adverse events should be followed until they are resolved or the patient's participation in the trial ends. Instructions for reporting changes in an ongoing adverse event during a patient's participation in the trial are provided in the instructions that accompany the adverse event case report forms.

In addition, all serious adverse events and those non-serious events assessed by the investigator as possibly related to the investigational product should continue to be followed even after the patient's participation in the trial is over. Such events should be followed until they resolve or until the investigator assesses them as "chronic" or "stable." Resolution of such events is to be documented on the appropriate CRF.

## 13. STATISTICAL METHODS

### 13.1 Sample size calculation

This is the second study with Iodinated Activated Charcoal for COPD in human subjects. The primary objective is to demonstrate drug performance with respect to lung function (change from baseline to 8 weeks in spirometry parameter FEV<sub>1</sub> baseline). Results from the previous study of IAC effect on COPD study was used to make sample size estimations for the present study:

#### Sample size estimation, absolute change from baseline, baseline as covariate

|                                      | Estimated difference | Residual SD | Effect size | n per group |
|--------------------------------------|----------------------|-------------|-------------|-------------|
| FEV <sub>1</sub> baseline (mL)       | 159                  | 184         | 0.869       | 23          |
| FEV <sub>1</sub> post-bronchodilator | 182                  | 202         | 0.902       | 22          |
| FVC baseline (mL)                    | 293                  | 313         | 0.937       | 20          |
| FVC post-bronchodilator (mL)         | 243                  | 391         | 0.622       | 43          |

2-sided t-test, significance level  $\alpha=0.05$ , power  $(1-\beta)=0.80$

Based on the calculations presented in the table above, sample size was set to 40 patients per treatment group. While a smaller sample size would have sufficed for the primary endpoint, sample size was increased in order to achieve precision in estimates of treatment effects for all spirometry parameters.

### 13.2. Summary statistics

In general, data will be presented by summary statistics which will include number of patients, mean, standard deviation, median, minimum and maximum for continuous data and frequency and percentage for categorical data.

### 13.3. Analysis Sets

The Safety Analysis Set will consist of all randomized patients that received any amount study medication.

The Full Analysis Set will include all subjects included in the safety set that were still on study medication at Visit 3 and have complete efficacy data (both baseline and 8 weeks) for at least one of the efficacy endpoints.

All efficacy analyses will be performed on the Full Analysis Set.

#### **13.4. Statistical Analyses**

Change from baseline to 8 weeks will be analyzed by and Analysis of Covariance (ANCOVA) including treatment and baseline value for the following efficacy endpoints:

- primary endpoints (FEV<sub>1</sub> and FVC)
- CAT (assessed at the clinic and average daily value of home assessments)
- St George's respiratory questionnaire

Absolute distance and change from baseline in distance covered during the six minute walk test will be compared between treatment groups using the Wilcoxon signed-rank test.

The number of patients with at least one thyroid hormone changing from normal at baseline to abnormal at 4 and 8 weeks will be compared using a Fisher's exact test and a 95% confidence intervals based on the Clopper Pearson method will be given for the proportions in each treatment group.

The correlation coefficient (Pearson's rho) will be computed between all pairs of efficacy endpoints.

#### **13.5. Statistical Issues**

All statistical testing will be performed at the 5% significance level. No adjustment for multiplicity of testing will be made.

Available data from prematurely withdrawn subjects will be included in the analysis as far as possible. Missing data will not be imputed.

#### **14. QUALITY CONTROL (QC) AND QUALITY ASSURANCE (QA)**

The trial will be conducted in compliance with this protocol, ICH GCP and applicable requirements. The distribution, deliveries, storage and returns of the investigational medicine product will be handled according to the guideline of ICH GCP.

Monitoring visits to the trial site will be made regularly during the trial, to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of agreement with data on Case Report Forms. The investigator/institution guarantees access to source documents by Norma Lund AB and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by Norma Lund AB as well as inspection by appropriate regulatory agencies.

It is important that the investigator and the relevant personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

## **15. STOPPING RULES / DISCONTINUATION CRITERIA**

The sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of Patients, but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the investigator must contact all participating Patients within one week.

## **16. ETHICS**

### **16.1 Ethical Conduct of the Trial**

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18<sup>th</sup> World Medical Assembly, Helsinki, Finland, 1964 and later revisions, ICH guidelines and GCP.

### **16.2 Independent Ethics Committee (IEC) and regulatory review**

It is the responsibility of the investigator to obtain approval from IEC of the trial protocol/amendments, the final version of the informed consent form and other written information provided to the patients. The investigator should file all correspondence with the IEC. Copies of IEC approvals should be forwarded to Norma Lund AB.

It is the responsibility of the sponsor to obtain approval from the national regulatory authorities of the trial protocol/amendments. The distribution of these documents will be handled by the sponsor.

Any amendment must be approved by regulatory authorities and ethical review board before implementation. Sponsor will distribute any subsequent amendment and new version of the protocol to the principal investigator.

Sponsor will provide ethical review boards, national regulatory authorities and principal investigators with safety updates/reports according to local requirements.

### **16.3 Patient Information and Consent**

It is the responsibility of the investigator to give each patient prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The patient must be given opportunity to ask questions and allowed time to consider the information provided. The patients must be informed about their right to withdraw from the trial at any time. Written patient information must be given to each patient before enrollment. Furthermore, it is the responsibility of the investigator to obtain signed informed consent from all patients prior to inclusion in the trial. Investigator must ensure that the

original signed informed consent is stored in the investigator study file and a copy of the signed informed consent form is given to the patient.

#### **16. 4 Insurance**

All patients in this study are covered by the Swedish Pharmaceutical Insurance. In addition, the patients are covered by insurance in LIF.

## **17. DATA HANDLING AND RECORD KEEPING**

### **17.1 Case Report Forms**

A CRF should be completed for each included patient and electronically transferred to the server of the data management centre. Case Report Forms (CRF) will be used and all data including the patient's diary sheet will be collected. The completed original CRFs are the sole property of PharmaLundensis AB and should not be made available in any form to third party, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from PharmaLundensis AB.

### **17.2 Record Retention**

To enable evaluations and/or audits from Health Authorities/Norma Lund AB, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and clinic records), all original signed Informed Consent Forms, and copies of all source data. To comply with international regulations, the investigator should retain the records for 15 years. Source document verification (SDV) will be performed by the trial monitor(s) for each patient participating in the trial.

## 18. REFERENCES

1. <http://www.who.int/mediacentre/factsheets/fs310/en/>
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the diagnosis, management and prevention of COPD; 2010.
3. Connors Jr AF, Dawson NV, Thomas C, Harrell, Jr FE, Desbiens N, Fulkerson WJ et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. *Am J Respir Crit Care Med* 1996;959-67.
4. Henning K-D and Schäfer S. Impregnated activated carbon for environmental protection. *Gas Sep Purif* 1993 Vol 7(4):235-240.
5. Henning K-D, Keldenich K, Knoblauch K, Degel J. Impregnated activated carbon for mercury removal. *Gas Sep Purif* 1988;2.March.
6. Skogvall S, Korsgren M, Grampp W. Evidence that neuroepithelial endocrine cells control the spontaneous tone in guinea pig tracheal preparations. *J Appl Physiol.* 1999 Mar;86(3):789-98.
7. Skogvall S, Erjefält JS, Olin AI, Ankerst J, Bjermer L. Oral iodinated activated charcoal improves lung function in patients with COPD. *Respir Med.* 2014 Jun;108(6):905-9. doi: 10.1016/j.rmed.2014.03.001. Epub 2014 Mar 12.
8. Nicola JP, Basquin C, Portulano C, Reyna-Neyra A, Paroder M, Carrasco N. The Na<sup>+</sup>/I<sup>-</sup> symporter mediates active iodide uptake in the intestine. *Am J Physiol Cell Physiol.* 2009 Apr;296(4):C654-62. doi: 10.1152/ajpcell.00509.2008.
9. Wolff J. Perchlorate and the thyroid gland. *Pharmacol Rev.* 1998 Mar;50(1):89-105.
10. Spitzweg C1, Dutton CM, Castro MR, Bergert ER, Goellner JR, Heufelder AE, Morris JC. Expression of the sodium iodide symporter in human kidney. *Kidney Int.* 2001 Mar;59(3):1013-23.
11. Greer MA1, Goodman G, Pleus RC, Greer SE. Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. *Environ Health Perspect.* 2002 Sep;110(9):927-37.
12. Bernecker C, Intermittent therapy with potassium iodide in chronic obstructive disease of the airways. A review of 10 years experience. *Acta Allergol* 1969;24(3):216-25.
13. Rogers DF. Mucoactive drugs for asthma and COPD: any place in therapy? *Expert Opin Investig Drugs* 2002 jan;11(1):15-35).

## **19. APPENDIX**

**Appendix 1.** Complete list of reported side effects in COPD study PL1101.

**Appendix 2.** Abnormal thyroid hormone values in the IAC group in PL1101.

**Appendix 3.** Complete list of reported side effects in CFS study PL1201

**Appendix 4.** Thyroid hormone values in the IAC group in PL1201