Revised Non-Interventional Study (NIS) Protocol	
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Outcome study following reimbursement changes in the use of fixed combination inhalers in patients with asthma or COPD in Iceland

Sponsor: ***AstraZeneca AB***

AstraZeneca Nordic

[redacted]

[redacted]

AstraZeneca Research and Development site representative

[redacted], Value Demonstration Manager Date

Study Delivery Team Leader

AstraZeneca Nordic, [redacted]

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1.0	[redacted]		
2.0	[redacted]		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change

NON-INTERVENTIONAL STUDY PROTOCOL SYNOPSIS (*IF APPLICABLE)*

Outcome study following reimbursement changes in the use of fixed combination inhalers in patients with asthma or COPD in Iceland

National Co-ordinating Investigator of the Non-Interventional Study

[redacted]

Principal Investigator of the Non-Interventional Study

[redacted]

Advisory Board members of the Non-Interventional Study

[redacted]

[redacted]

[redacted]

[redacted]

Study Site(s), number of patients and countries planned

This is a retrospective database study that will be conducted by the University of Iceland.

Planned number of patients is 6000.

Total planned Study period	
Estimated date of first data collection	[redacted]
Estimated date of last data collection	[redacted]
Estimated date of data base lock	[redacted]

Medicinal Products (type, dose, mode of administration) and concomitant medication

Not applicable.

Rationale for this Non-Interventional Study (NIS)

For patients requiring maintenance treatment with both ICS and LABA to control their asthma or COPD, combination inhalers, such as Symbicort Turbuhaler or Seretide Diskus, are

convenient, may increase compliance, and ensure that the LABA is always accompanied by an ICS.

Iceland has a population of approximately 350 000 people. The asthma prevalence is around 5-6 % and the COPD prevalence is 18 %. It is estimated that approximately 7000 patients in Iceland were treated with fixed combination treatment at the end of the year 2009.

A change in the reimbursement for asthma and COPD medications took place on 1 January 2010 in Iceland. The reason for the change was to reduce the costs of asthma and COPD medications. It is anticipated that this has lead to a switch from fixed combination treatments (ICS and LABA) to other treatment regimens such as corticosteroids alone, often in spray inhaler (PMDI) rather than Discus or Turbuhaler, and/or β-adrenergic drugs as mono-components (SABA or LABA) in approximately half of the patients during 2010. It is important to investigate how this change has influenced the quality of treatment and outcome for the patients.

This study aims to describe the outcomes associated with the change in reimbursement. The study will be a database study which will include all patients who were on treatment with ATC code R03 and/or have the diagnosis code J44 or J45 in the medical record database Saga®, the pharmaceutical registry or the primary care registry used for data collection.

Objectives of this Non-Interventional Study

The primary objective of this NIS is:

- To investigate how a switch from fixed combination treatment (ICS and LABA) to other treatments influence asthma or COPD treatment failure

The secondary objectives of this NIS are:

- To map out the development of asthma and COPD treatment in Iceland after the change in reimbursement

- To investigate health economic outcomes

Study design

All patients on treatment with ATC code R03 and/or diagnosis code J44 or J45 according to the medical record database Saga® or the registries used will be included in this retrospective, database audit study.

Clinical data will be extracted from the medical records registry, Saga® by the Saga administrator from Landspitali and Laeknastrid and by Directorate of Health from primary care registry. Data on drug use will be collected from the Directorate of health drug registry. Data will be collected for the time period [redacted].

The merging of data will be performed by the Directorate of Health.

Study variable(s):

Primary endpoint

A composite endpoint of treatment failure defined as:

- Exacerbations
- All contacts with Health Care Professionals
- Number of patients switched back to fixed combination or other add on treatments

Secondary endpoints

The secondary endpoints of this study will be:

- Number of patients switched from fixed combination to other treatment regimens
- Number of patients with inhaled corticosteroids and short acting bronchodilator mono-components(dose and strength)
- Number of patients with inhaled corticosteroids and long acting bronchodilator mono-components (dose and strength)
- Difference between prescribed and collected medication
- Co-morbidities
- Resource use following forced switch of medication

Statistical methods

Cox regression and Poison regression for match pairs will be used in the analysis, using the non-switched patients as a reference group to establish any year to year difference in the combined event rate. Environmental effects will in this way be eliminated.

Continuous and nominal variables will be described using standard statistical measures, i.e. number of observations, number of missing observations, mean, standard deviation, minimum and maximum value, median, 1st and 3rd quartile.

All categorical variables will be summarized with absolute and relative frequencies.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this NIS Protocol.

Abbreviation or special term	Explanation
ADR	Adverse Drug Reaction
Assessment	An observation made on a variable involving a subjective judgement (assessment)
AZ	AstraZeneca
CRO	Clinical Research Organisation
National Coordinator	The National Coordinator is the main line of contact to coordinate the submissions and responses of the Leading Ethics Committee and of the Ethics Committees related to the other participating sites (Non-Leading Ethics Committees).
NIS	Non-Interventional Study
NISP	Non-Interventional Study Protocol
NISR	Non Interventional Study Report
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
Variable	A characteristic of a property of a patient that may vary eg, from time to time or between patients

1. INTRODUCTION

1.1 Background

Asthma is a chronic respiratory disease of the airways in which many inflammatory cells and cellular elements are involved. The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. Effective control of asthma symptoms and maintenance of optimal lung function are critical for the long-term management of patients with persistent asthma. Management of asthma requires long-term monitoring and medical care with treatment based on severity of symptoms and level of lung function.

Asthma guidelines recommend adjustment in treatment to achieve control of day to day symptoms and to reduce future risk of complications, i.e. asthma exacerbations (1). Treatment to achieve this is based on a treatment ladder using a stepwise approach. In mild-to-moderate persistent asthma one option is to first treat with a low dose of an inhaled glucocorticosteroid (ICS) with the addition of a short-acting β2-adrenoceptor agonist (SABA) for symptom relief. If the patients are inadequately controlled by this initial treatment the next step may be to either increase the dose of the ICS or to add a long-acting inhaled β2-agonist (LABA) for regular use.

For patients with persistent asthma, current treatment guidelines also recommend maintenance treatment with ICS in combination with a LABA for asthmatics uncontrolled by inhaled ICS alone (step 2 to step 3). Combination therapy with ICS and LABA represents a major improvement in the treatment of asthma and is used increasingly as fixed-combination therapy (1).

Chronic Obstructive Pulmonary Disease (COPD) is a chronic slowly progressive disease characterized by airflow limitation, i.e. loss of lung function. Most of the lung function impairment is fixed, although significant reversibility is usual and can be produced by pharmacological treatment. COPD is a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease for years and die prematurely from it or its complications.

Combination therapy with inhaled corticosteroids and LABA in a single inhaler has been reported to substantially reduce the rate of exacerbations of COPD and improve the heath related quality of life. Consequently, such combination therapy has been recommended by the Global Initiative for Chronic Obstructive Lung Disease guidelines, (evidence A) for patients with FEV1<50% of predictive and have frequent acute exacerbations of COPD (i.e., ≥1 exacerbation/year) (2). Switching patients' inhalers without their consent may diminish the self-control associated with good asthma management, leave the doctor-patient relationship damaged, increase resource utilization, and waste medication (3).

1.2 Rationale for conducting this NIS

For patients requiring maintenance treatment with both ICS and LABA to control their asthma or COPD, combination inhalers, such as Symbicort Turbuhaler or Seretide Diskus, are convenient, may increase compliance, and ensure that the LABA is always accompanied by an ICS.

Iceland has a population of approximately 320 000 people. The asthma prevalence is around 5-6 % and the COPD prevalence is 18 %. It is estimated that approximately 7000 patients in Iceland were treated with fixed combination treatment at the end of the year 2009.

A change in the reimbursement for asthma and COPD medications took place on 1 January 2010 in Iceland. The reason for the change was to reduce the costs of asthma and COPD medications. It is anticipated that this has lead to a switch from fixed combination treatments (ICS and LABA) to other treatment regimens such as corticosteroids alone, often in spray inhaler (PMDI) rather than Discus or Turbuhaler, and/or β-adrenergic drugs as mono-components (SABA or LABA) in approximately half of the patients during 2010. It is important to investigate how this change has influenced the quality of treatment and outcome for the patients.

This study aims to describe the outcomes associated with the change in reimbursement. The study will be a database study which will include all patients who were on treatment with ATC code R03 and/or have the diagnosis code J44 or J45 in Landspitali and Laeknasetrid medical record database Saga®, the pharmaceutical registry or the primary care registry used for data collection.

2. NIS OBJECTIVES

2.1 Primary objective

The primary objective of this NIS is:

- To investigate how a switch from fixed combination treatment (ICS and LABA) to other treatments influence asthma or COPD treatment failure by a composite assessment of:
    - Exacerbations defined as use of oral steroids and/or emergency room visits and/or hospitalizations
    - Contacts (visit/phone) with Health Care Professionals
    - Changes in inhaled treatment

2.2 Secondary objectives

The secondary objectives of this NIS are:

- To map out the development of asthma and COPD treatment in Iceland after the change in reimbursement by:

- Describing patients switched and non-switched
- Investigating if prescribed new treatment is equivalent to the previous fixed combination treatment
- Analyze any gaps between prescribed drugs and collected drugs at pharmacy
- Describe co-morbidity

- To investigate health economic outcomes

3. STUDY PLAN AND PROCEDURES

This Non-Interventional Study Protocol has been subject to an internal review according to AstraZeneca standard procedures.

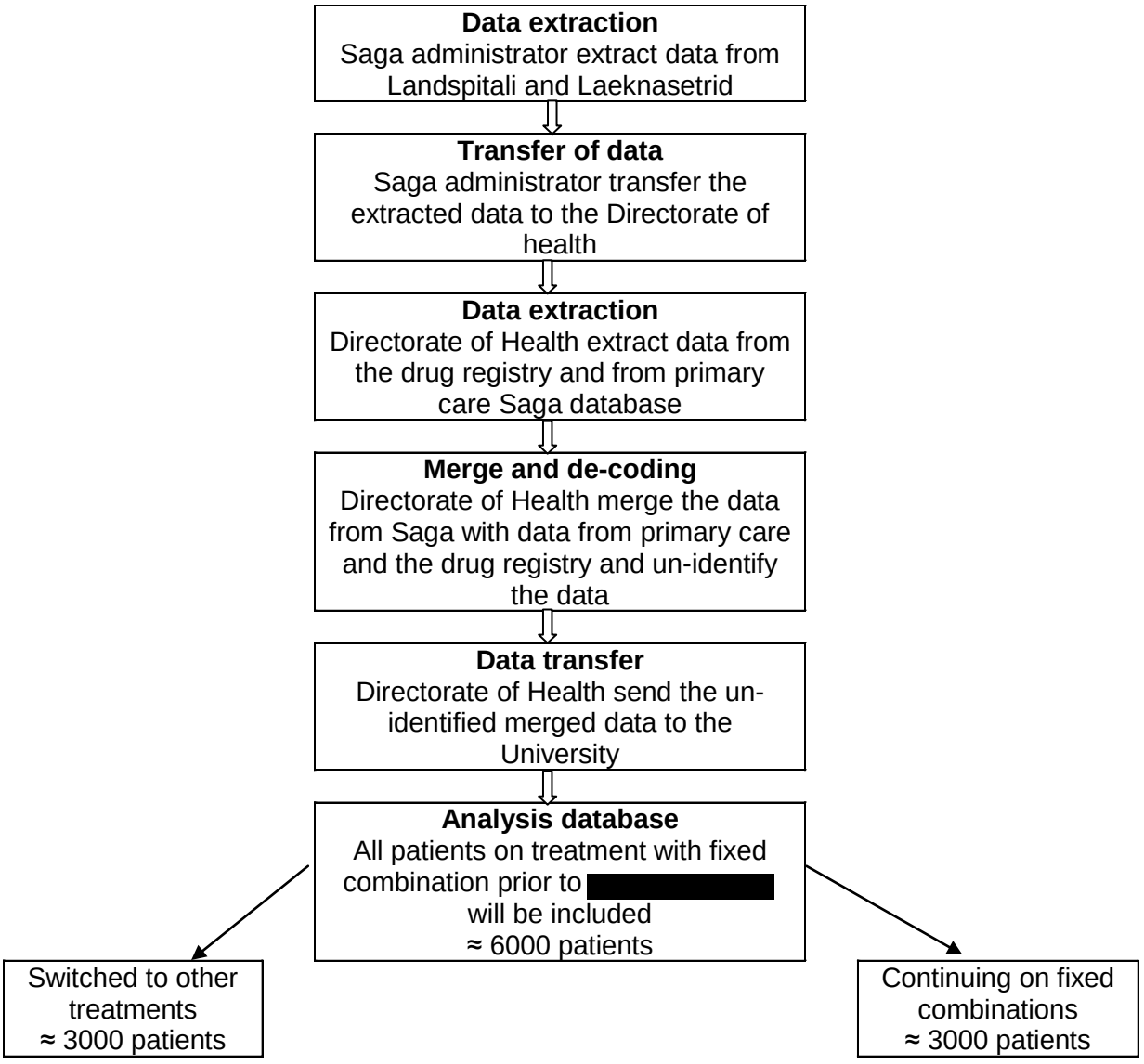
3.1 Overall study design and flow chart

All patients on treatment with ATC code R03 and/or diagnosis code J44 or J45 according to the medical record database Saga® or the registries used will be included in this retrospective, database audit study.

Clinical data will be extracted from the medical records registry, Saga® by the Saga administrator from Landspitali and Laeknastrid and by Directorate of Health from the primary care registry. Data on drug use will be collected from the Directorate of health drug registry. Data will be collected for the time period [redacted].

The merging of data will be performed by the Directorate of Health.

Figure 1 Study Flow Chart



4. SELECTION OF PATIENT POPULATION

4.1 Investigators

This is a retrospective database study that will be conducted by the University of Iceland.

Estimated number of patients on fixed inhalation treatment is 6 000 patients. It is estimated that half of these patients has been switched to other treatment regimens.

4.2 Inclusion criteria

The patient population and their retrospective data records that will be observed in this study must fulfil the following criteria:

1. All patients who was on treatment with fixed combination asthma or COPD therapy by [redacted]

4.3 Exclusion criteria

None.

5. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

All patients on treatment with R03 and/or diagnosis code J44 or J45 will be identified in the Saga database or in registries used. The study population will be patients treated with fixed combination asthma or COPD therapy by [redacted] according to data from Saga, primary care registry and the drug registry.

5.1 Primary endpoint

A composite endpoind of treatment failure defined as:

- Exacerbations (use of oral steroids and/or emergency room visits and/or hospitalizations
- All contacts with Health Care Professionals
- Number of patients switched back to fixed combination or other add on treatments

5.2 Secondary endpoints

The secondary endpoints of this study will be:

- Number of patients switched from fixed combination to other treatment regimens
- Number of patients with ICS and SABA mono-components (dose and strength)
- Number of patients with ICS and LABA mono-components (dose and strength)
- Number of patients with other treatments
- Difference between prescribed and collected medication
- Co-morbidities
- Resource use following forced switch of medication

5.3 Data collected from medical records

Saga® is a medical records database used by primary care, specialist care and hospital care in Iceland. The database is hosted on a central server. Principal Investigator will apply for necessary approvals prior to data collection. Data from Landspitali and Laeknasetrid will be extracted by the Saga administrator for the time period [redacted]. Data from primary care registry will be collected by Directorate of Health. The following data will be extracted:

- Demographic data (gender, year of birth)
- All diagnosis and date of diagnosis
- Assessment of treatment failure according to definition
- Asthma and COPD medication
- Concomitant medication
- Health care resource use

5.4 Data from the Directorate of Health register on drugs

The following data regarding drugs will be obtained from the Directorate of health register on drugs collected from pharmacy for the time period [redacted]:

- Date of prescriptions
- Date of collection
- Drug names
- Drug cost
- Strengths
- Number of doses in device
- Prescribed doses per day

5.5 Health Economic measurements and variables

Health care resource use will be calculated as contacts with primary care center, contacts with specialist and number of in-hospital time periods for asthma or COPD and pharmacological treatment.

6. SAFETY REPORTING

6.1 NISs without a specific safety objective

Due to the non-interventional character of this study, no pro-active safety data collection should take place. Only spontaneously mentioned safety events should be reported as required by the post-marketing pharmacovigilance regulations. The method for reporting spontaneously mentioned safety events are described below. It is of the outmost importance that all staff involved in the study is familiar with the content of this section. The investigator is responsible for ensuring this.

6.1.1 Definition of Adverse Drug Reactions (ADR)

An ADR is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product, suspected to be causally related to the product

6.1.2 Reporting of spontaneously mentioned adverse drug reactions

With regards to the reporting of ADRs observed in patients participating in this study, the following guideline applies: ADRs should be reported to Health Authorities as stated in local regulations and/or, if the investigator considers it appropriate, to AZ (in case of an ADRs of an AZ-product) or the corresponding marketing authorization holder of the drug.

7. ETHICAL CONDUCT OF THE NON-INTERVENTIONAL STUDY

The Non-Interventional Study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GCPs and the applicable legislation on Non-Interventional Studies.

The Principal Investigator at the University will perform the NIS in accordance with the regulations and guidelines governing medical practice and ethics in the country of the NIS and in accordance with currently acceptable techniques and know-how.

7.1 Ethics review

The final protocol of the Non-Interventional Study must be approved or given a favourable opinion in writing by the Ethics Committee.

The Ethics Committee must also approve any amendment to the protocol according to local regulations.

7.2 Patient data protection

The NIS data will be stored in a computer database at the University, maintaining confidentiality in accordance with the local law for Data Protection.

8. STUDY MANAGEMENT BY ASTRAZENECA

8.1 Monitoring, Quality Control and Archiving

Before any data is collected for the purpose of this study, the local MC representative or delegate will:

- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regards to protocol compliance, and the responsibilities of AstraZeneca or its representatives.

During the study the local MC representative or delegate can implement different activities to assure compliance with AZ standards of quality.

8.2 Training of study site personnel

The Principal Investigator will ensure that appropriate training relevant to the NIS is given to investigational staff, and that any new information relevant to the performance of this NIS is forwarded to the staff involved.

8.3 NIS timetable and end of study

Before first data collection in the NIS and any NIS related procedures are undertaken the following should be fulfilled

- Written approval of the NIS by the Ethics Committee and, according to local regulations
- Approval from Data Protection Board
- Proper agreements between AstraZeneca and the Principal Investigator is signed

The planned timetable for the NIS is estimated to be as follows:

- First data collection – [redacted]
- Last data collection – [redacted]
- NIS Report – [redacted]

Should AstraZeneca decide to discontinue the study prior to what was established in this protocol, the investigator, and relevant authorities should receive written notice describing the reasons why the study was terminated at an earlier date.

9. DATA MANAGEMENT

9.1 Collection, monitoring, processing of data and archiving

All patients treated with ATC code R03 and/or diagnosis J44 or J45 will be identified in the Saga medical records database by the Saga administrator. Study data, see 5.3, will be extracted for all identified patients together with their personal id number. Extracted data will be saved to a disk and securely transferred to the Directorate of Health by the Saga administrator.

The Directorate of Health will identify all patients treated with ATC code R03 and/or diagnosis J44 or J45 in the pharmaceutical registry, see 5.4, and the primary care registry, see 5.3 and merge the data from all data sources. All personal data will be deleted and each patient will be given a study number. The code key will be kept at the Directorate of Health. The unidentified data will be sent to the Principal Investigator at the University of Iceland.

The anonymous database with the merged data will be hosted at the University of Iceland and will be made available to a statistician from AstraZeneca Nordic for analysis. The database

will be stored at the University for 5 years after study completion. The identification key at the Directorate of health will be destroyed according to their routines.

All study documentation will be archived at the university for 2 years after study completion.

Study completion will be defined as date of Last Data Collection.

9.2 Reporting and publication of data

- AstraZeneca will prepare a Non-Interventional Study Report within 12 months after completion of the last patient.
- The Medical Director, the NIS Study Leader and the National Coordinator will be the signatory of the report

AstraZeneca is obliged to analyse and report all NIS data as described in the protocol.

In accordance with the Declaration of Helsinki, both authors and publishers have ethical obligations. In publication of the results of the NIS, the authors are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. AstraZeneca endeavours to publish the results of NIS and is committed to ensure that the data are reported in a responsible and coherent manner.

AstraZeneca seeks to ensure that publications in biomedical journals follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in *its Uniform Requirements of Manuscripts Submitted to Biomedical Journals*.

AstraZeneca is committed to ensuring that authorship for all publications should comply with the criteria defined by the ICMJE. These state that: "*Each author should have participated sufficiently in the work to take public responsibility for the content*."

AstraZeneca believes that participation solely in the collection of data or drafting the manuscript does not justify authorship. These conditions apply equally to external investigators and to AstraZeneca employees.

Other members of the group should be listed in the acknowledgments as appropriate.

Publication of data subsets from individual institutions participating in multicentre studies should not precede the primary manuscript, and when developed should always reference the primary publication of the entire study.

10. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

10.1 Statistical evaluation – general aspects

The general analytic approach (Cox and Poison regressions) assumes a constant event rate in the different time periods. The analysis will start by controlling this assumption.

10.2 Descriptive statistics

Continuous and nominal variables will be described using standard statistical measures, i.e. number of observations, number of missing observations, mean, standard deviation, minimum and maximum value, median, 1st and 3rd quartile.

All categorical variables will be summarized with absolute and relative frequencies.

10.3 Determination of sample size

It is estimated that approximately 3000 patients have had their fixed combination treatment (ICS + LABA) withdrawn.

The combined event rate is the yearly rate of percent of patients with the sum of the events of oral steroids, hospitalizations, contacts with Health care professionals, change of treatment, and usage of antibiotics.

A two group chi-2 test with a two-sided significance level will have 80% power to detect the difference between a percent of the combined event rate of 20.0% before the switch and a combined event rate of 24.3% after the switch (odds ratio of 1,284) when the sample size is 1500 and the significance level is 5%.

Since this is a retrospective study, the sample size calculation is not a formal calculation; it's more used as an indication of the magnitude of the possible findings with a sample size of in total 1500 patients. If the sample size is decreased the change in the combined event must be larger to get a statistical significant change in this rate.

10.4 Statistical analyses

The data from the non-switched patients will be analyzed to establish, if there are any differences between the year 2010 and the previous time period. If the rate of the combined rate is unchanged between the years measured as time to first event, no correction will be done. The data from the non-switched patients will also be analyzed to see if there are any difference between the different month and dates. If there is a marked effect on specific dates during 2010 with high event rates, a sensitivity analysis will be made where these dates will be removed from the database from all years in the one analysis and by keeping these dates in another analysis. If there is a marked month-to-month effect this will be compensated by selecting the same time periods from the different years using a sensitivity approach. If the

difference in event rate is different from zero, this effect will also be included in the analysis Cox and Poison regressions as described in the following. .

The same patient will have information before the switch and after the switch. The combined endpoint of time to first event will be analyzed with methods for survival data (Cox regression models, Kaplan-Meier estimates) including a possible year effect. The PROC GENMOD will be used with the Wald (default) and the binary option for calculating standard errors taking the matched pairs advantage into the calculation (3). The analysis will be done with time to event as the dependent variable and with time period as factor and total time in study as an offset variable.

The Cox regression will be repeated for each of the components in the combined end-point, e.g. hospitalizations, prescription of oral steroids, prescription of antibiotics, unplanned visits and change of asthma or COPD drug.

The total number of events of the combined end-point will be analyzed by a Poison regression (using PROC GENMOD with the Wald and the poison option and the matched pair advantage) with number of events as the dependent variable and the time period factor and total time in study as an offset variable. The confidence limits and the p-value will be adjusted for overdispersion.

The total ICS dose before and after the switch will be compared by an ANOVA with time period as the dependent variable and time period and patient as fixed factors and the repeated option on the patient level. Equivalent values of the different ICS drugs will be used in the comparison.

All analysis will be done for all diagnosis combined, and will also be analyzed divided into the patients primary diagnosis code, asthma or COPD, while COPD patients also switched from Spiriva to other treatments will be treated as a separate group, excluded from the main analysis and analyzed using the previous mentioned methods.

11. LIST OF REFERENCES

1. GINA. Global Strategy for Asthma Management and Prevention 2008

2. Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Version updated Sept. 2005. Available from http:// www.goldcopd.com

3. Doyle S et al. What happens to patients who have their asthma device switched without their consent? Prim Care Respir J. 2010 Jun;19(2):131-9.

4. Alexander M. T. and, J A. Kufera Butting Heads on Matched Cohort Analysis Using SAS® Software. NESUG 2007. 1-12.