AstraZeneca

Non-Interventional Study (NIS) Report

NIS Name/Code	NIS-RRU-DUM-2010/1
Edition Number	<<>>
Date	08 11 2011

Non-interventional retrospective multicenter study of patients with bronchial asthma during a routine visit to out of patients' clinics (NIKA)

Study dates: 30.11.2010 – 06.05.2011(LSV)

First Subject In: 24 December 2010

Last Subject Last Visit: 06 May 2011

Associated Document: T15 NIS Report (NISR), ed 1.0
Template Active Date: May 2010
8-P85-1-X Planning, Approval, Conduct and Reporting of Non-Interventional Studies (NISs)

TABLE OF CONTENTS PAGE

LIST OF APPENDIX

1. STUDY SITES

The study was conducted to assess the level of control over bronchial asthma (BA) in 1000 patients from 26 outpatient treatment facilities in 12 cities of the Russian Federation.

2. PUBLICATIONS

After the end of the study analyzed all study data and will be prepared the final report of research by AstraZeneca or authorized company officials.

3. STUDY DATES

First Subject In: 24 December 2010

Last Subject Last Visit: 06 May 2011

4. BACKGROUND AND RATIONALE

There exists a limited number of pharmacoepidemiological studies conducted in Russia so far with the aim to assess the quality of asthma pharmacotherapy and the level of asthma control [1,2,3]. All those studies (such as FEDA-2000 [1], NABAT [2], IKAR [3], and Bronchial Asthma in Russia [4]) demonstrated that the overall level of asthma patients' care is still far from being optimal, while the structure of medical prescriptions is often inconsistent with international guidelines or national standards of asthma pharmacotherapy.

Most patients in such studies had low asthma control, numerous exacerbations and a high rate of hospitalizations. Furthermore, official statistics shows that there remain high rates of mortality (over 750 cases per year) and disability among asthma patients [1].

Since recent years have seen a number of positive trends in asthma patients' care have been objective:

1. Prescription structure with an increased percentage of state-of-the-art combined medications providing a potentially higher level of asthma control [1,7,8].
2. Availability of Russian versions of questionnaires (Asthma Control Questionnaire (ACQ), Asthma Control Test (ACT) allowing quantitative evaluation of asthma control) [9,10].
3. Changes in the very concept of asthma control: the new 2009 International Guidelines [11**]**

indicate that it is necessary to assess **overall asthma control** made up of symptom control and reduction of potential future risks [11].

There have been no studies conducted in Russia so far investigating the upgraded of the overall asthma control, while the most recent national study assessing the quality of asthma patients' medical care was performed as far back as in 2006 [4]. Russian healthcare professionals have to deal with the lack of pharmacoepidemiological data, as opposed to the other countries have a large experience gained in pharmacoepidemiological evaluation of asthma management, and quite a number of large-scale studies have been conducted looking at asthma control level (e.g. Asthma in America [12], AIRE [13], INSPIRE [14]).

The above reasons warrant initiating a multicenter national study in asthma patients in order to assess overall asthma control in the real-life clinical practice for the first time in Russia. Such a study will for the first time allow determine overall asthma control which is characteristic for the Russian population of asthma patients as well as identifying potential regional differences in asthma control. Performing such a study will make it possible to identify treatment approaches that offer optimal asthma control and to provide a pharmacoepidemiological description of difficult patients' categories with low asthma control.

5. OBJECTIVES

Primary objective

The main objective of the study is to assess asthma control in Russian asthma patients according to the new criteria provided in the international guidelines, such as Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice, 2009 [11] and identify pharmacological approaches that provide a higher level of overall asthma control.

Additional objectives:

- to determine the main demographic, clinical and pharmacoepidemiological characteristics of low-controlled patients.
- to assess comparative value of the Asthma Control Questionnaire (ACQ) and Asthma Control Test (ACT) with regard to their use in clinical practice in Russia

6. STUDY DESIGN AND SELECTION CRITERIA

Study design

The study conducted during a routine visit of patients to out of patients' clinics.

Patients are to be included into the study after they have provided informed consent to collection and further processing of data obtained. The data provided by patients are not to be analysed by investigating physicians and will have no effect on further management of the patients. Patients included into the study received treatment in routine clinical settings and in accordance with the current treatment standards in Russia.

The inclusion of patients into the study was occur during their routine visits to out-patients' clinics. Only those patients who meet all of the inclusion criteria and none of the exclusion criteria could be included into the study. After providing their informed consents, patients were asked to fill in a number of questionnaires:

- the Russian version of the 5-item Asthma Control Test (ACT)
- the Russian version of the 5-item Asthma Control Questionnaire (ACQ)
- and a questionnaire containing data on gender, age, disease duration
  severity of various symptoms and the number of recent exacerbations and hospitalizations.

The questionnaires are to be self-completed by patients. Patients will be allowed to ask their investigating physician questions or request clarifications while completing the questionnaires. In such cases, the physician should provide all the necessary clarifications without, however, prompting the patients to choose certain answers. After completion of the questionnaires, the investigating physician is to ensure that all the items have been fully completed. Erroneous entries must be crossed out and corrected in a way that excludes ambiguous interpretation of the answers obtained.

Patients completed the study after filling out the questionnaires.

Each investigator completed a specially designed questionnaire, allowing collecting information on patient diagnosis, concomitant diseases, spirometric data and therapy for bronchial asthma.

Table 1 Study plan

	Visit 1
Study participants исследования	
Informed consent	X

Control of inclusion/exclusion criteria	X
Patient questionnaire	X
Investigator questionnaire	X

SELECTION OF STUDY POPULATION

Investigators

The investigators are selected by education, training, experience and availability of time to perform the study. 35 outpatient physicians are to enroll approx. 1,050 subjects (enrollment of patients were competitive among the sites) in the 14 cities in Russian Federation (Moscow, S.-Petersburg,Novosibirsk, Irkutsk, Omsk, Krasnoyarsk, Perm, Chelayabinsk, Krasnodar, Rostov-na-Dony, Ekaterinburg, N.Novgorod, Samara, Ufa).

Inclusion Criteria

All patients should meet the following criteria:

1. Male and female patients > 18 years of age.
2. Patients with asthma diagnosed in accordance with the Global Initiative for Asthma (GINA [xv]) within 6 months before inclusion into the study
3. Patients who signed their informed consents to collection and further processing of data on their disease course
4. Patients with no changes in their treatment within 2 months before inclusion into the study.

Exclusion Criteria

The conditions below are considered exclusion criteria:

- Asthma patients with an exacerbation at the moment of inclusion
- Pregnant women
- Patients on β-blockers

Patients with (based on medical records):

- COPD, mucoviscidosis or bronchiectasis
- Severe heart failure (NYHA functional class III-IV)
- Renal insufficiency
- (endogenous creatinine >150 mmol/L)
- Cancer
- Previous stroke

- Patients following a major surgery
- Hepatic insufficiency

  (AST or ALT >2-fold ULN)

7. TARGETED PATIENT POPULATION

The targeted study population includes subjects aged ≥ 18 years who have been receiving drug therapy for asthma for 6 months. Patients must provide their informed consents and fulfill all the study procedures.

Patients who fail or are unable to provide their informed consents will not be included into the study.

8. CRITERIA FOR EVALUATION (MAIN VARIABLES)

Primary variable:

The number and % of patients with well-control asthma according to Global Initiative for Asthma (GINA) criteria; scores from the completed Asthma Control Test (ACT); scores from the completed Asthma Control Questionnaire (ACQ).

Other variables:

- Demographic patient characteristics: age, gender, social status
- Smoking
- Data of history: date of diagnosis of asthma, severity of asthma, the date of spirometry testing
- Asthma control: controlled asthma, partly controlled asthma, uncontrolled asthma
- Data of the disease: the presence and manifestation of symptoms of asthma in the past week, the use of an inhaler to relieve asthma symptoms during the last week, the impact of asthma on the patient's daily activities over the past week, the number of asthma exacerbations in the last year.
- Concomitant diseases: coronary heart disease, hypertension, arrhythmias, allergic rhinitis, chronic sinusitis, gastric ulcer/duodenal ulcer, chronic gastroesophageal reflux disease and obesity.
- The duration of therapy asthma, the regularity of reception of prescribed drugs by patients
- Therapy of asthma: a combination therapy, inhaled corticosteroids (ICS), oral corticosteroids, b2-agonists long-acting, b2-agonists short-acting, short-acting M-anticholinergic and drugs of other groups (trade name, daily doses).
- Results of questionnaires: ACQ and ACT

Availability of emergency calls, missing work/study for the last year

9. STATISTICAL METHODS

Statistical evaluation – general aspects

Patient demographics and average levels of asthma control were processed by descriptive statistic methods. Patients grouped based on treatment they are receiving. The null hypothesis is that the patient groups receiving different treatment do not differ in their number of exacerbations and hospitalizations within the previous 6 months or in asthma control as assessed using questionnaire scores. ANOVA [16] and Kruskal-Wallis [17] analysis of variance by ranks used to test the null hypothesis. The risk of exacerbation and hospitalization were assessed according to treatment administered with generation of contingency tables analyzed using Fisher's exact test.

9.1 Population Analysis Sets

9.1.1 Definition of the target population

Patients were enrolled from December 2010 to May 2011 and the enrollment was finished after inclusion of 1000 patients. Synergy Research Group, the contract research organization, carried out control over the study progress and compliance with Good clinical practice guidelines (GCP) and also verification of medical data indicated in a case report form.

The following measures were applied as primary variables:

1. Percentage of patients achieved *control over symptoms* according to GINA guidelines [1];
2. Percentage of patients achieved *overall BA control*: controlled bronchial asthma at the moment of examination and absence of any exacerbations of the disease for the previous year.

Anthropological parameters of patients, data on current therapy pattern and percentages of patients with different BA control level were calculated and processed using methods of descriptive statistics. Percentages of patients with controlled bronchial asthma, obtained by different estimation methods (regular doctor's assessment, patients' self-evaluation, ACQ-5 and ACT questionnaires) were compared by using Fisher's test with results of symptoms assessment and spirometry data according to GINA guidelines (the gold standard of control evaluation accepted in this study) [1]. ACQ-5 and ACT tests findings were interpreted in pursuance of criteria mentioned in Table 1.

Table 1. Interpretation of ACQ-5 and ACT tests findings.

Asthma control index	Asthma control level according to GINA		
	Controlled asthma	Partially controlled asthma	Uncontrolled asthma
ACT	≥20	19-16	≤15
ACQ-5 [i]	≤0.75	0.75-1.5	≥1.5

To assess the impact of different schemes of BA baseline therapy on odds in achieving control patients with moderate and severe disease were divided into four groups by the pattern of prescribed therapy: only inhaled glucocorticosteroids treatment, administration of free-dose and fixed-dose combinations of inhaled glucocorticosteroids (ICS) and long-acting β-agonists, Symbicort single inhaler therapy. The null hypothesis consisted in absence of differences in control level between patients receiving various treatments. Odds on achieving control over symptoms and overall control over bronchial asthma in these groups were compared by using Fisher's test and odds ratio. Additional comparisons of various valuables were made with the help of Wilcoxon test for paired comparisons.

9.2 Statistical Analysis Results

9.2.1 Descriptive Analysis:

1000 patients were included in the study from 26 centers of 12 cities of the Russian Federation: Ekaterinburg, Irkutsk, Krasnodar, Krasnoyarsk, Moscow, Nizhny Novgorod, Novosibirsk, Perm, Rostov-on-Don, Saint Petersburg, Ufa and Chelyabinsk.

Average age of patients included into the studies was 50 years old (from 18 till 85 years). Men made up twenty nine percent of the population. The average disease duration was 12.9 years (from 0.5 till 75 years). As of the time of inclusion into the study all patients received treatment of bronchial asthma for at least one year, on the average 9.7 years (from 1 till 61 years).

Severe form of the disease was reported in 15% of patients, 68% and 17% of patients had moderate and mild severity of the disease, respectively. In 165 patients (16.5% of the total amount) had disability for bronchial asthma, 56.9% of the study participants were in employ, 6.2% of participants were students, other 5.9% of study participants reported they were unemployed, and 31% of participants drew an old age pension.

Seventy one percent of the study participants were never-smokers, 19.2% were tobacco users in the past, and 9.8% continued smoking at that moment.

The patients enrolled into the study received different treatment including therapy which was inconsistent with existing recommendations, for example, inhaled glucocorticosteroids were not administered in some patients with persistent asthma (6%), and combination medications (inhaled glucocorticosteroid and long-acting β2-agonist) were prescribed to 34% of patients with mild severity of bronchial asthma.

In general, the most common method of maintenance therapy turned out to be the administration of fixed-dose (46% of patients) and free-dose (11% of patients) combinations of inhaled glucocorticosteroids and long-acting β2-agonists. Budesonide/formoterol (Symbicort) single inhaler therapy was taken by 8% of the study participants. Percentage of inhaled glucocorticosteroid monotherapy comprised 21% of prescribed treatment; other 11% of patients received bronchial spasmolytics only. Systemic glucocorticosteroids were administered in 3% of patients.

9.3 Overall level of control over bronchial asthma symptoms

In the study population the overall control over bronchial asthma was achieved in 13.4% of cases. In patients with mild form of the disease the overall control was indicated in 20% of cases, and in moderate and severe form of bronchial asthma it was in 12% and 9% of cases, respectively.

Significantly more patients (23%) had controlled asthma according to GINA guidelines [1], partially controlled bronchial asthma was detected in 35% of the study participants. In patients with more severe form of bronchial asthma the control over symptoms was significantly lower than in those with mild forms of the disease (see Figure 1). Thus, patients with moderate bronchial asthma had 2.3 times less odds on good control over the illness in comparison with patients with mild form of bronchial asthma (OR 2.3 [1.53 - 3.47], $P<0.001$). And for patients with severe form of bronchial asthma odds on good control proved to be even more lower: 2.7 times less than in those with moderate form of bronchial asthma (OR 2.7 [1.88 - 3.77], $P<0.001$) and 6.1 times less relative to patients with mild form of bronchial asthma (OR 6.1 [3.75 - 10.02], $P<0.001$).

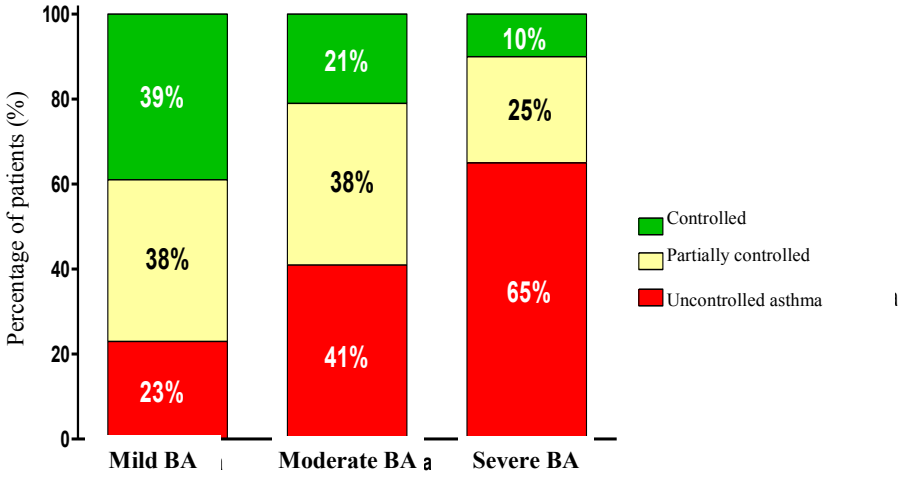

Figure 1. Control over bronchial asthma symptoms depending on severity of the disease.

Among patients with disease duration from one till three years the percentage of individuals with uncontrolled bronchial asthma worked out 27%. In patients suffering from asthma during four till twenty years this measure persisted on higher but almost constant level (from 39 till 42% of patients with uncontrolled bronchial asthma). And only in patients with more than twenty years duration of the illness substantial growth of uncontrolled bronchial asthma prevalence was reported (from 52 till 55%).

Patients who started baseline therapy more than two years after symptoms onset, had by 31% more odds on uncontrolled BA comparing with those who began to get their therapy in first two years after the disease manifestation (OR 1.31 [1.005 - 1.696]; P=0.0452).

9.4 Comparison of various methods of symptoms control assessment

During the study the control over symptoms was determined by different methods in the same patients: [15] exact to GINA guidelines [15] (data provided by patients in their answers for questionnaire items and spirometry measures were used); [12] control assessment by the regular doctor; [13] ACT; [18] ACQ-5.

The assessment of control according to GINA guidelines was used as a reference estimation method. Relating to this method, the most approximate results of control diagnostics were provided by ACQ-5 test: the level of well-controlled bronchial asthma was not significantly different in applying GINA guidelines and ACQ-5 (see Figure 2). In the meantime, regular doctors' assessments and ACT results were significantly different from evaluation according to GINA guidelines and produced more overstated results of control over symptoms (see Figure 2).

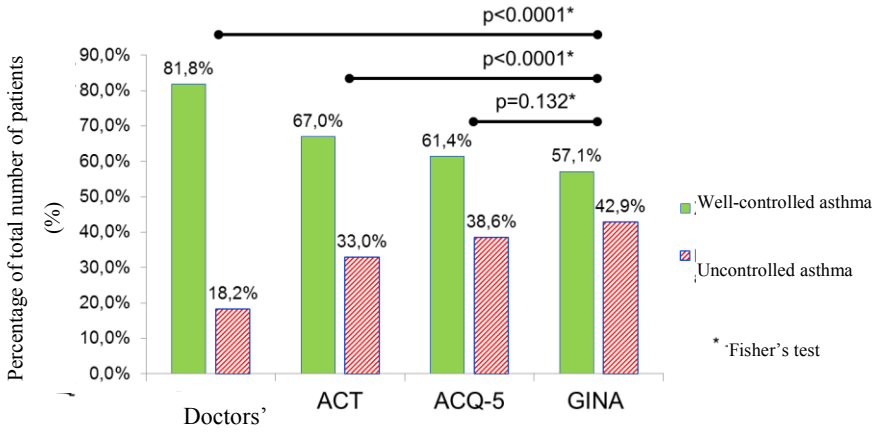

Figure 2. Diagnostics of well-controlled and uncontrolled bronchial asthma by different methods in comparison with assessment according to GINA guidelines [1].

Control level assessment according to GINA guidelines coincided with evaluation on ACQ-5 in 64% of all cases, with evaluation on ACT in 60% of cases and with regular doctors' assessment in 51% of cases only. Concerning diagnostics of uncontrolled bronchial asthma, the highest degree of sensitivity was demonstrated by ACQ-5 questionnaire, and the lowest degree of sensitivity is indicated in regular doctor's assessment (see Table 2).

Table 2. Sensitivity and specificity of uncontrolled asthma assessment.

	ACT	ACQ-5	Regular doctor's assessment
Sensitivity	72.4%	81.3%	38.6%
Specificity	95.8%	92.0%	96.4%
Positive predictive value	If a patient has ACT ≤15, odds of uncontrolled asthma are 91.6%.	If a patient has ACQ ≥1.5, odds of uncontrolled asthma come up to 87.8%.	If the doctor diagnoses lack of control, odds of uncontrolled asthma make 88.5%.
Negative predictive value	If a patient has ACT >15, odds of well-controlled asthma are 82.7%.	If a patient has ACQ <1.5, odds of well-controlled asthma come up to 86.9%.	If the doctor diagnoses good control over BA, odds of good control make 68.4%.

While analyzing errors in control level determination, it turned out that doctors in the majority of cases overstated asthma control level: 86% of all misjudgments committed by physicians in evaluation of control over symptoms lied in diagnostics of the higher control in comparison with GINA guidelines (see Table 3). Errors in using ACT also demonstrated overrated level of

control in 90% of cases. Assessment performed on ACQ-5 proved to be not only closer to GINA guidelines, but also were lack of systematic error with false upward bias of BA control level.

Table 3. Errors of asthma control evaluation.

Evaluation of control over asthma	Control assessment methods		
	Physicians' assessment	ACT	ACQ-5
The evaluation corresponds to GINA guidelines (in % to total amount of tests)	51	60	64
Evaluation provides higher control level than GINA guidelines (in % to total amount of tests)	42	36	20
Evaluation provides lower control level than GINA guidelines (in % to total amount of tests)	7	4	16

9.5 Patient's self-evaluation of control over bronchial asthma

Questionnaire survey revealed patients' inclination to overrate significantly their level of control over bronchial asthma. For instance, among patients with uncontrolled asthma 76% of respondents estimated their condition as partial control over the illness, and among patients with partial control over the disease more than third of patients reported that their bronchial asthma was fully controlled (see Figure 3).

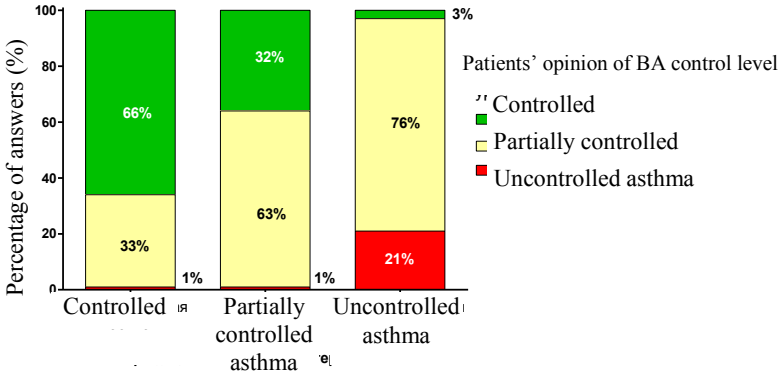

Figure 3. Patient's self-evaluation of asthma control level.

9.6 Impact of therapy on control level

The assessment of the impact of different baseline therapy schemes on control level was made in 834 (83%) patients with moderate and severe bronchial asthma. For this purpose, the patients were divided into four groups by the pattern of prescribed therapy: only inhaled

glucocorticosteroids treatment (n=108), administration of free-dose (n=457) and fixed-dose (n=108) combinations of inhaled glucocorticosteroids (ICS) and long-acting β-agonists, budesonide/formoterol (Symbicort) single inhaler therapy (n=83). Groups were not significantly different by bronchial asthma severity.

The highest measures of control over bronchial asthma were reported in subgroup of patients received budesonide/formoterol (Symbicort) single inhaler therapy, that is both for baseline therapy and for relief of symptoms (see Figure 4). Generally, odds to have control over bronchial asthma symptoms in the group of single inhaler turned out to be 96% higher than in applying any other therapy (OR 1.96 [1.189-3.219]; P=0.0135). But along with this, there were not obtained statistically significant distinctions in the level of control over symptoms in usage of single inhaler and fixed-dose combinations treatment.

Odds on achieving overall control over bronchial asthma in the group of single inhaler proved to be two-fold higher than in groups with other treatment (OR 2.16 [1.237-3.763]; P=0.009). Especially substantial differences occurred in achieving control between using Symbicort single inhaler therapy and treatment of free-dose combinations (more than 9 times much), see Figure 5.

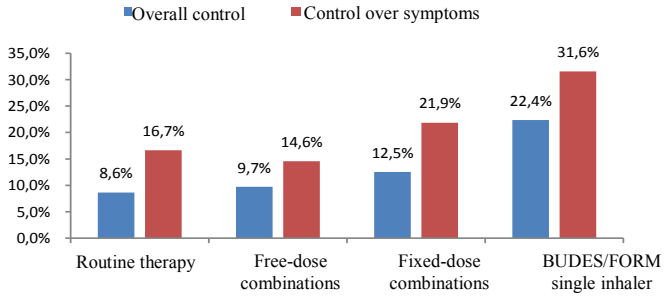

Figure 4. Percentage of patients achieved overall control and control over BA symptoms under various baseline therapies.

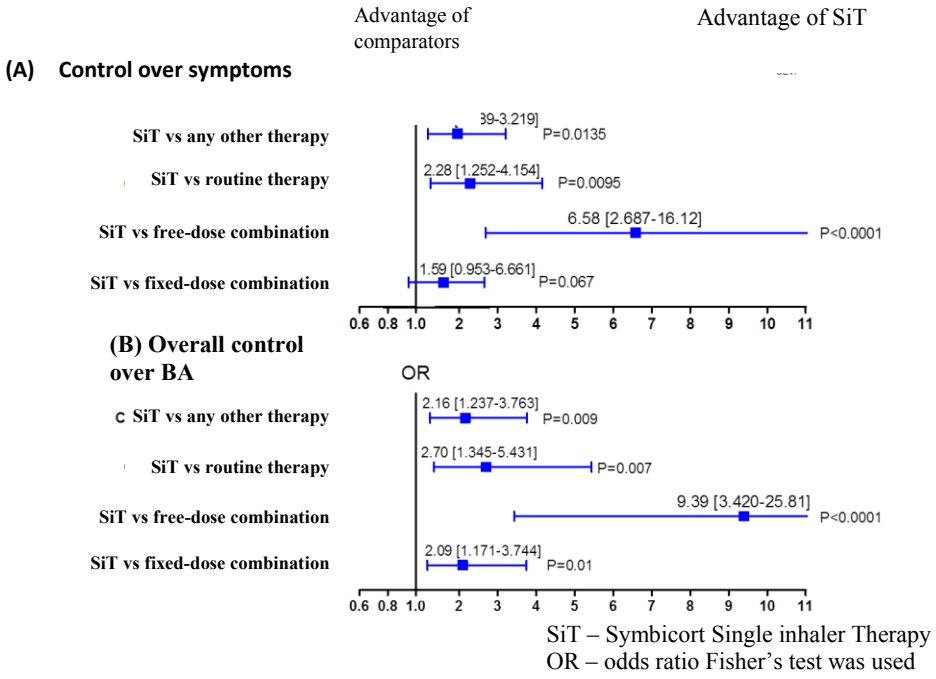

Figure 5. Odds ratio of achieving overall control over BA (A) and control over symptoms (B) in applying Symbicort Single inhaler Therapy (SiT) in comparison with other therapy approaches.

9.7 Therapy efficiency assessment and its optimization

On the whole, only 4% of patients (among patients with uncontrolled bronchial asthma – up to 10%) considered their treatment was ineffective, other 34% of patients indicated insufficient efficacy of therapeutic interventions. Consequently, the majority of patients regardless of BA control level believed their current therapy was appropriate. Among regular doctors the rate of negative evaluations of current therapy found to be significantly higher – 12%, but at that time 42% of the study participants needed to increase extent of therapy in concordance with GINA guidelines.

Nevertheless, the decision to change the therapy was made in 44.7% of cases. In patients with controlled asthma the treatment was modified in 14% of cases, moreover, by this was meant increase in extent of treatment almost in all cases. Generally, only in 0.4% of cases the extent of therapy was reduced comparing with the previous one. In patients with uncontrolled bronchial asthma their treatment was changed in 71% of cases.

When changing therapy, it was most of all concerned with shifting of patient from inhaled glucocorticosteroids therapy to fixed-dose (44%) or free-dose (10%) combinations of inhaled glucocorticosteroids and long-acting β-agonists. In other 37% of patients the dose of inhaled

glucocorticosteroids was raised, and in 8.6% of patients treatment change included addition of prolonged theophyllines or antileukotrienes.

10. ETHICS

10.1 Ethics review

The final protocol of the Study, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by the Independent Ethics Committee (IEC).

10.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki and ICH GCPs (International Conference on Harmonisation of Technical Requirements for registration of Pharmaceutical for Human Use – Good Clinical Practice) and the local regulatory requirements as well as biomedical ethical principles accepted in AstraZeneca.

11. DATE OF THE REPORT

08 November 2011

12. REFERENCES

1. Чучалин А.Г. и др. Фармакоэпидемиология детской астмы: результаты многоцентрового российского ретроспективного исследования (ФЭДА - 2000). Пульмонология. 2001 (www.antibiotic.ru).
2. Чучалин А.Г. и др. Базисная терапия тяжелой бронхиальной астмы у взрослых. Данные национального исследования НАБАТ. Пульмонология 2004; 6:68-77.
3. Чучалин А.Г. и др. Качество жизни больных БА в России: результаты многоцентрового популяционного исследования. Атмосфера 2003; 3-48.
4. Чучалин А.Г. и др. Бронхиальная астма в России: результаты национального исследования качества медицинской помощи больным бронхиальной астмой. Пульмонология 2006; 6: 94-102.
5. Здоровье населения России и деятельность учреждений здравоохранения в 1999-2002 г. (статистические материалы). - М.: МЗ РФ, 2003.

6. Bousquet J. et al. Budesonide/Formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respire. Med. 2007; 101:2437-2446

7. Bateman E.D. et al. Overall asthma control: The relationship between current control and future risk. J. All. Clin. Immunol. 2010; 125(3):600-608.

8. Huchon G. et al. Lung function and asthma control with beclomethasone and formoterol in a single inhaler. Respi. Med. 2009; 103(1):41-9

9. Juniper E.F.et al. Development and validation of a questionnaire to measure asthma control. Eur. Respir. J. 1999; 14: 902-907

10. Nathan R.A. et al. Development of the Asthma Control Test: a survey for assessing asthma control. J. All. Clin. Immunol. 2004; 113:59 – 65.

11. Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice. Am. J. Respir. Crit. Care. Med.2009; 180: 59–99.

12. Asthma in America (www.asthmainamerica.com)

13. Rabe K.F. et al. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. Eur. Respir. J. 2000; 16: 802-807.

14. Partridge M.R. et al. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. BMC Pulm. Med. 2006; 13: 6 - 13.

15. Global Strategy for Asthma Management and Prevention (GINA), 2009 (http://www.ginasthma.org)

16. ANOVA - ANalysis Of VAriance between groups

(http://www.physics.csbsju.edu/stats/anova.html)

17. Kruskal-Wallis one-way analysis of variance

(http://udel.edu/~mcdonald/statkruskalwallis.html)

18 Gené RJ et al. ERS Conference 2009; Poster 3050