№3 Том5 2017

Фармакоэкономика
теория и практика

Pharmacoeconomics
theory and practice

№3 Volume5 2017

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PHARMACOECONOMIC ANALYSIS OF CONTINUATION OF USE OF SYMBICORT® TURBUHALER® AS THE SOLE INHALER FOR BRONCHIAL ASTHMA THERAPY

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Summary: *Control of bronchial asthma (BA) is a key principle of disease treatment. One of the factors resulting in uncontrolled BA is incorrect use of an inhalation device and, as a consequence, low adherence to therapy. According to research data, up to 94% of patients, depending on the type of delivery system, make mistakes during application, resulting in inconsistent dosage and reduced efficacy. These factors may contribute toward an increase in costs of the healthcare system and decrease in the quality of life of patients. For example, an unapproved change of the inhaler may lead to reduced BA control and, as a result, growing expenses for medical services despite lower initial costs of pharmacotherapy. Availability of a wide range of medications and devices for delivering them, as well as limited financial resources of the healthcare system inspired a pharmacoeconomic assessment of various schemes of BA therapy. According to the cost analysis results, the provided amounts of direct and indirect costs for one-year therapy with Symbicort® Turbuhaler® as the sole inhaler is on average 4.5% lower than the costs of treatment with DuoResp Spiromax®, Formisonid-Nativ®, Foradil Combi®, Foster®, Seretide® and Seretide® Multidisk®. A budget impact analysis demonstrated that switching of patients from therapy with budesonis/formoterol Turbuhaler® as the sole inhaler to therapy with DuoResp Spiromax®, Formisonid-Nativ®, Foradil Combi®, Foster®, Seretide® and Seretide® Multidisk® entails additional average budget expenditures of RUB 4 mln per annum due to increased hospitalization frequency per 106 cases, more frequent calls for ambulance per 364 cases, more frequent visits to outpatient settings and polyclinics per 180 cases, as well as more days of temporary disability per 1 862 days - every figure given per 1,000 patients with BA. It is, therefore, clinically and economically reasonable that patients initially receiving Symbicort® Turbuhaler® as a support maintenance therapy to continue therapy using the same medication.*

Key words: control of bronchial asthma, budesonid/formoterol, Symbicort SMART, Turbuhaler, exacerbations, change of inhalers, budget impact analysis, costs analysis, pharmacoeconomics

Introduction

The main objective of treating bronchial asthma (BA) of any severity is to achieve and maintain control over clinical manifestations of the disease and reduce future risks of exacerbations [1]. An important task is to prevent exacerbations as they constitute the cause of disease progression leading to decreased quality of life and significant increase in BA treatment costs. The inhalation system of delivery plays a significant role in achieving control of BA. However, inhalation devices are manifold and each has its own specifics and requires individual training in using it. Incorrect inhalation technique may cause not only inconveniences in using the device leading to low adherence to the therapy, but also variable dosage and side effects. In view of the above, it can be concluded that the efficacy of BA therapy depends on the choice of the inhalation device and may lower after unauthorized replacement of the device [3, 10].

A replacement of the inhalation device without consultation with the physician may lead to: incorrect use of the inhaler, low adherence, decrease of pulmonary deposition, increase in exacerbations/lower control of the pulmonary disease [2]. The effects of unauthorized change in the medication delivery device on the BA control was also studied in detail by Thomas M. et al. (Fig. 2) [3]. A cohort study which lasted for 2 years and compared 824 patients, who changed the type of device for ICS delivery without consultations with physicians, with 824 patients, who continued using their usual devices. The results demonstrated that a switch to a different inhalation device leads to an increased number of patients with uncontrolled BA and decreased number of patients with controlled asthma [3].

Besides, the consequences of an unauthorized switch to a different inhaler or inhalation device should be compared to the arguments in favor of changing the inhalation device without the patient's consent in terms of non-medical/budget expenses. For example, initial decrease in costs may be associated with further growth of healthcare expenses [4]. Björnsdóttir U.S. et al. [4] Systematic Review data prove that an unauthorized switch to different inhalers by patients is associated with a series of negative results of treatment - both at the individual level and at the level of the organization. These factors reducing therapy adherence may result in increased costs of the healthcare system and decreased quality of the life of patients [4]. Following the trend of reducing the expenses in the context of limited healthcare resources, additional investments designed to ensure high adherence to therapy result in reduced need for healthcare resources. On the contrary, reduced costs of purchasing medications when switching to a different inhalation device may lead to higher future healthcare expenses caused by a decrease in BA control (Fig.1) [4].

Thus, the hypothesis that a change in the inhalation device to the one included into the compensation program (based solely on economic parameters) may lead to increased need of such patient for medical assistance, thus resulting in growing healthcare expenses served the grounds for performing of this pharmacoeconomic study.

The objective of the study was defined as an assessment of the economic benefits of a change in therapy with Symbicort® Turbuhaler® medication to therapy with DuoResp Spiromax®, Formisonid-Nativ®, Foster®, Foradil Combi®, Seretide® and Seretide® Multidisk®.

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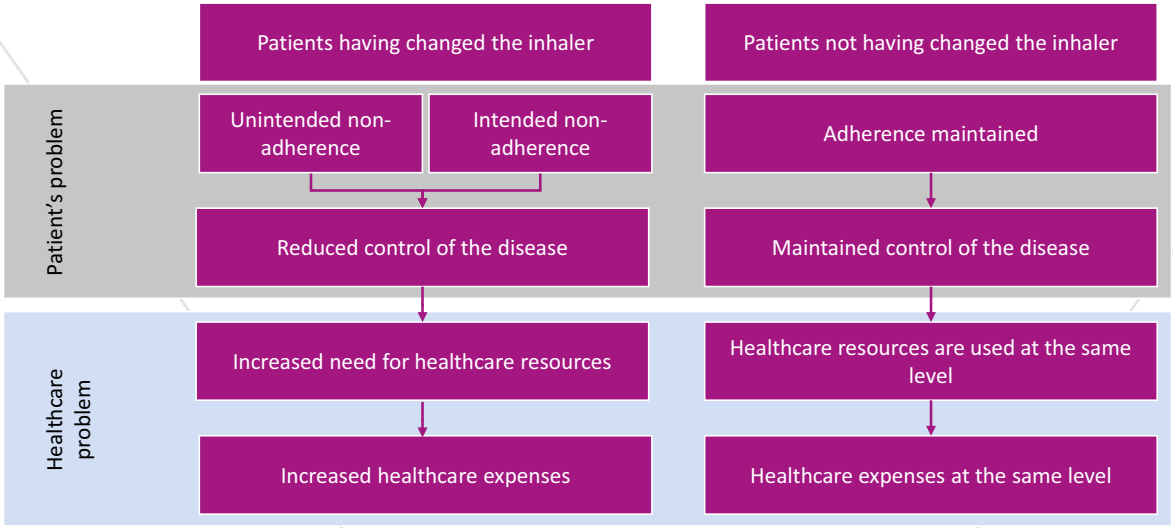


Figure 1. Impact of a change in the inhalation device on healthcare costs

Material and methods

Based on the above listed hypothesis and study objective, we performed pharmacoeconomic assessment of using Symbicort® Turbuhaler® medication as maintenance and reliever therapy versus using DuoResp Spiromax®, Formisonid-Nativ®, Foradil Combi®, Foster®, Seretide® and Seretide® Multidisk®.

During our study, we reviewed the following two scenarios of replacing Symbicort® Turbuhaler® medication with other inhalers from the standpoint of impact on achieving BA control and reducing exacerbations (Figure 2). We calculated the frequency of drawing on healthcare resources for each of the scenarios on the bass of the data about the share of patients with various levels of BA control. This was the basis for calculating expenses and performing the budget impact analysis.

The first scenario was based on comparing fixed combinations of Budesonid and Formoterol used as a sole inhaler for maintenance and reliever therapy. For example, using Markov's model based on the study by Thomas M. et al. [3], we assessed the impact of switching patients from Symbicort® Turbuhaler® to Formisonid-Nativ® and DuoResp Spiromax® medications on BA control and healthcare budget expenses. In the second scenario, we compared Symbicort® Turbuhaler® with other medications belonging to the group of inhaled gluco-corticosteroids in combination with long-acting beta-2-agonists (ICS/LABA): Foradil Combi® (budesonid/formoterol), Foster® (beclomethasone/formoterol), Seretide® and Seretide® Multidisk® (salmeterol/fluticasone). Symbicort® medication was used as the sole inhaler (i.e., in the SMART mode - Symbicort Maintenance and Reliever Therapy). In case of using other medications, Ventolin (Salbutamol), the short-acting beta-2-agonist (SABA), was used for quick relief. All known generics/Symbicort® analogues (characterized by the same INNs but different delivery systems) were, therefore, included into the first part of the study as reference drugs. Medications from the ICS/LABA group with the biggest market share (as per the IMS Health database) were included into the second part of the study. Foradil Combi® was included into the second reference group despite the same INN for the following reasons: This medication is not a classic fixed combination and has no recommendations for use as maintenance and reliever therapy. Information about the number of patients achieving BA control was obtained from the NIKA trial [21, 36]. The simulation time was 1 year and hence no discount was used. According to the selected clinical trials and the pharmacoeconomic study design, the target population was defined as adult patients over 18 with a proved diagnosis of moderate to severe BA requiring 3-4 stage GINA therapy, currently using Symbicort® Turbuhaler® as the sole inhaler [18, 21, 36].

Data Sources

At the first phase of the pharmacoeconomic study, we performed a data search for publications relating to the topic of the study. The search request was designed based on the following key words: "asthma", "clinical trial", "maintenance and reliever therapy", "budesonide/formoterol", "Symbicort Turbuhaler", "Symbicort SMART", "Spiromax", "Inhaler CDM",

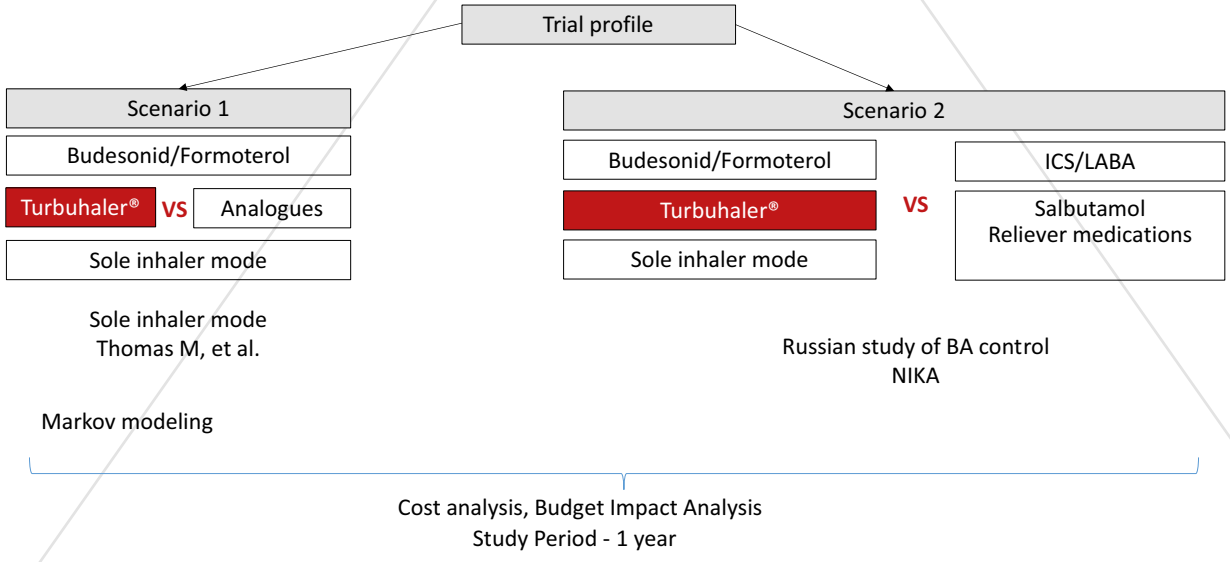


Figure 2. Study Design

"Aerolizer", "beclomethasone/formoterol or Foster", "inhaler technique", "combined therapy", "asthma control", "compliance", "inhaler switching", "switching therapy", "exacerbations", "salmeterol/fluticasone or Seretide". For reviewing publications, data search was performed in the following databases: "Rossiyskaya Meditsina" (Russian Medicine) database of the Central Scientific Medical Library of I.M. Sechenov First Moscow State Medical University, scientific electronic library elibrary.ru. We also used free data search resources such as Yandex, Google, etc. The search was based on the following key words: "bronchial asthma", "combined therapy", "inhaled gluco-corticosteroids", "ICS/LABA", "bronchial asthma control", "budesonide/formoterol", "Symbicort Turbuhaler", "SMART", "inhaler switching", "DuoResp Spiromax", "Fomisonid – Nativ", "beclomethasone/formoterol", "Foster", "salmeterol/fluticasone", "Seretide", "Foradil Combi", "Aerolizer", "exacerbations", etc.

During the search, more than 1 000 publications were identified as meeting the search criteria. Then we excluded the duplicate publications and research materials irrelevant to BA therapy with budesonide/formoterol as the sole inhaler and ICS/LABA medications described above. We also excluded publications of preliminary results from further search. In order to be included into the study, the "results" section should have contained data on the number/frequency of exacerbations detailing relevant outcomes, level of BA control (shares of patients achieving control), death rate, side effects frequency or quality of life for each of the compared alternatives. The level of evidence was determined according to the grading scales used to assess the levels of evidence of the results of clinical trials of medications and evidence credibility levels. Studies with A or B level of evidence (evidence summarized in a systematic review or meta-analysis and evidence from prospective RCTs, respectively) were selected in the first place. In the absence of the above, studies with lower level of evidence were analyzed. The Results were summarized in a special table for further analysis and the assessed by experts. After such screening, we selected 22 publications for further review (Table 1). All publications referred to patients with moderate to severe BA requiring 2-4 stages of GINA therapy. As we can see from the Table, the majority of authors, e.g., Stallberg B. et al. [32], Bateman E. D. et al. [18], Reddel H. K. et al. [19] and others compare Symbicort® Turbuhaler® in the SMART mode with fixed combinations of medications containing budesonide/formoterol. In most cases, the respective medication was delivered with a Turbuhaler® device. When the alternative therapy was selected based on the best clinical practices (standard therapy) – Demoly P. et al. [20] and Sears M. R. et al., 2008 [22], the researchers did not provide any data about specific medications from the ISCS/LABA group. The publications assessing the inhaling technique which we managed to find (Sandler N. et al., 2016 [38] and Rootmensen G. N. et al., 2010 [40]) did not cover all analyzed devices.

We did not find any studies which would assess the efficacy and safety of generics/ Symbicort® Turbuhaler® analogues used for maintenance and reliever therapy. As a consequence, we used the Markov modeling method, which demonstrated the impact of switching patients to an analogous inhalation device. We used the previously described study Thomas M. et al. [3] to assess the degree of impact of a change in the inhalation device. Based on the study design, the patients were achieving BA control with Symbicort® Turbuhaler® administered in the SMART mode. That is why we used BA control data from study Bateman E. D. et al. [18] as a natural progression for building the model. The study won the priority over the other meta-analyses as it contained data on the probability of shifting from one level of BA control to a different level thereby optimizing the process of building the model.

To perform a pharmacoeconomic assessment under the second scenario, we selected the Russian study NIKA [21, 36] as the only alternative reflecting the relevant schemes of comparison to the fullest extent possible. The distribution of shares of patients by levels of BA control was as follows: Symbicort® Turbuhaler® in SMART mode – 22.4%, salmeterol/fluticasone - 10.6%, any fixed combinations - 9.7%, any free combinations - 8.6% [21, 36]. Because no separate numerical data for each of the free/fixed combinations covered by the study were provided, we proceeded from the assumption that the values specified for the overall group corresponded to those for Foradil Combi® and Foster®. We also made the assumption that salmeterol/fluticasone delivered with a dosing aerosol inhalation device (DAI) or powder-based inhalation device (PBI) (Seretide® and Seretide® Multidisk®) were equally effective. Our assumption was based on the lack of data to the contrary.

It should also be noted that, during the data search, we did not find any studies with a simultaneous comparison of alternative medications in question, either for the first or second scenario, by frequency and type of adverse events (e.g., pharyngitis rate, nausea rate, etc.). For that reason, for the purposes of our pharmacoeconomic study, we used the adverse effects frequency provided in patient information leaflets of the compared alternatives [11-17].

Table 1. Results of the data search

No.	Author, year	Brief description / design, duration	Comparison alternatives	Rescue medications	Efficacy criterion
1	Bateman E. D. et al., 2011 [18]	post-hoc analysis of 5 RTCs (n>12,000, age 4-89 years), 6-12 months	BUD/FOR in SMART mode h.d. BUD + SABA e.d. BUD/FOR (Symbicort®) + SABA h.d. BUD/FOR (Symbicort®) + SABA h.d. SAL/FL (Seretide®) + SABA	Terbutaline (Bricanyl) 0.4 mg	level of BA control by GINA criteria and ACQ-5 (Asthma control) Questionnaire; Reduction of exacerbations progression risk
2	Reddel H. K. et al., 2011 [19]	post-hoc analysis of RTCs (n=12,507, age 4-89 years), 612 months	BUD/FOR in SMART mode h.d. Budesonide + SABA e.d. BUD/FOR (Symbicort®) + SABA h.d. BUD/FOR (Symbicort®) + SABA h.d. SAL/FL (Seretide®) + SABA	Terbutaline (Bricanyl) 0.4 mg	exacerbations frequency; using rescue medications, URTI progression rate (without separate date for each type)
3	Demoly P. et al., 2009 [20]	high level analysis of 6 open RCTs (n = 7,855, age above 12 years), 6 months	BUD/FOR in SMART mode the best clinical practices (ICS, ICS/LABA, ALTR [antagonists of leukotriene receptors], Xanthines and others + SABA)	Salbutamol, Terbutaline or Formoterol	exacerbations frequency; peak expiratory flow rate; BA control as per ACQ-5 questionnaire; use of rescue medications (number of patients making < 4 puffs per week); safety (AE [adverse events] frequency)
4	Arckhipov V.V. et al., NIKA, 2011 [21,36]	assessment of various types of baseline therapy impact on the BA control level; single-step polling of visitors in healthcare centers of various levels in several regions of the RF (n = 1,000, age above 18 years)	ICS; s/c: ICS + LABA (16% - Foradil Combi®); f/c: ICS + LABA (36% - Seretide®) and 2% - Foster®) and BUD/FOR SMART (Symbicort® - 62%)	n/a	share of patients who achieved control over symptoms as per the GINA criteria; share of patients who achieved overall BA control: controlled BA as of the moment of examination and no exacerbations of any kind during the preceding year, when control over symptoms was assessed using different methods for one and the same patients (in accurate compliance with GINA criteria, control assessed by attending physician, assessment per criteria of ACT [Asthma Control Test] Questionnaires and ACQ-5)

No.	Author, year	Brief description / design, duration	Comparison alternatives	Rescue medications	Efficacy criterion
5	Sears M. R. et al., 2008 [22]	randomized unmasked multi-center parallel group study (n = 1,538, age 12-94 years), 6 months	BUD/FOR SMART standard therapy (including ICS + LABA)	n/a	time until first severe exacerbation; number of severe exacerbations; average number of times of using rescue medications; EPS; ACQ-5 values; safety (serious AE [SAE] without specifying the type); amount of eosinophils in sputum
6	Hozawa S. et al., 2011 [23]	mono-center randomized unmasked clinical trial to study inflammation with small CIs, 4-8 weeks (n = 40)	BUD/FOR SMART SAL/FL	n/a	oscillation frequency (R5-R20); fractional exhaled nitric oxide (FeNO); BA control as per ACQ-5 questionnaire;
7	Scicchitano R. et al. (STAY), 2004 [24]	randomized double-blind parallel group study (n = 1,890, age 12-80 years), 12 months	BUD/FOR SMART h.d. ICS + SABA	Terbutaline	exacerbations frequency; use of rescue medications; AE frequency, EPS
8	Rabe K.F. et al. (STEAM), 2006 [25]	randomized double-blind parallel group study (n = 697, age 11-79 years), 6 months	BUD/FOR SMART BUD + SABA	Terbutaline 0.4 mg	duration and severity of exacerbations; FEV1, EPS, AE frequency number of days of BA control; number of days without BA symptoms;
9	Rabe K.F. et al. (SMILE), 2006 [26]	randomized multi-center parallel group study (n = 3,394, age 12-89 years), 12 months	BUD/FOR SMART BUD/FOR (Symbicort®) + SABA	Terbutaline, Formoterol	time until first exacerbation; exacerbations frequency; ACQ-5, AE frequency FEV1, EPS;
10	O'Byrne P.M. et al. (STEP), 2005 [27]	randomized double-blind multi-center parallel group study (n = 2,670, age 4-79 years), 12 months	BUD/FOR SMART BUD + SABA BUD/FOR + SABA all medications were delivered via a Turbuhaler® device	Terbutaline	FEV1, EPS; exacerbations frequency; use of rescue medications; AE frequency (without specifying the type)
11	Kuna P et al. (COMPASS), 2007 [28]	randomized double-blind double-masked parallel group study (n = 3,335, age above 12 years), 6 months	BUD/FOR SMART BUD/FOR f/c + SABA SAL/FL + SABA	Terbutaline	number of exacerbations; quality of life vallue as per AQLQ (Asthma Quality of Life Questionnaire); ACQ-5 values; FEV1; AE frequency (without specifying the type)
12	Bousquet J. et al. (AHEAD), 2007 [29]	randomized double-blind multi-center parallel group clinical trial with international participation (n = 2,309, 12-80, age 12-80 years), 6 months	BUD/FOR SMART SAL/FL + SABA	Terbutaline	time until first exacerbation; exacerbations frequency; AE frequency (without specifying the type)
13	Vogelmeier C. et al., 2005 [30]	randomized multi-center parallel group study (n = 2,143, age 12-84 years), 12 months	BUD/FOR SMART SAL/FL + SABA	Salbutamol (Ventoline)	time until first exacerbation; total number of severe exacerbations; FEV1; ACQ-5; AQLQ; safety (AE)
14	Edwards S.J. et al., 2010 [31]	meta-analysis of RTCs (n>12,000, age 4-89 years), 6-12 months	BUD/FOR in SMART mode h.d. Budesonide + SABA e.d. BUD/FOR (Symbicort®) + SABA h.d. BUD/FOR (Symbicort®) + SABA h.d. SAL/FL (Seretide®) + SABA	Terbutaline (Bricanyl) 0.4 mg	relative risk of exacerbations (indicating each outcome)
15	Stallberg B. et al., 2008 (SHARE) [32]	randomized unmasked multi-center parallel group study (n = 1,343, age above 12 years), 12 months	BUD/FOR SMART BUD/FOR f/c + SABA BUD/FOR s/c + SABA all medications were delivered via a Turbuhaler® device	Terbutaline	number of patients with at least 1 exacerbation during 1 year, number of SAE
16	Sears M. R. et al., 2009 [33]	meta-analysis of 6 RCT (n = 14,346), 6 months	BUD/FOR SMART BUD + SABA BUD/FOR f/c (Symbicort®) + SABA SAL/FL f/c + SABA	Terbutaline	Number of SAE; mortality
17	Kardos P., 2013 [34]	non-interventional study in real life (n = 482), 6 months	BUD/FOR SMART ICS/LABA s/c + SABA	n/a	AQLQ; exacerbations frequency;
18	Papi A. et al., 2013 [35]	randomized multi-center parallel group study (n = 1,714, age above 18 years), 12 months	BDP/FOR MART BDP/FOR f/c + SABA	Salbutamol	time until first exacerbation; number of exacerbations; number of rescue medication puffs; EPS; BA control

No.	Author, year	Brief description / design, duration	Comparison alternatives	Rescue medications	Efficacy criterion
19	Terzano C. et al., [37]	prospective study in real clinical practice (n = 1,070, age above 18 years), 12 months	BDP/FOR f/c BUD/FOR f/c SAL/FL f/c ICS; ALTR	n/a	exacerbations frequency; share of patients with BA control (as per ACT Questionnaire); quality of life as per EQ - 5D Questionnaire
20	Sandler N. et al., 2016 [38]	mono-center one-stage cross-over study (n = 120, age 18-69 years)	Turbuhaler® Spiromax® Easyhaler®	n/a	share of patients adhering to inhalation technique; number of mistakes in inhalation technique
21	Virchow C. et al., 2016 [39]	randomized double-blind double-masked controlled multi-center study (n = 574, age above 12 years), 12 weeks	BUD/FOR Turbuhaler® BUD/FOR Spiromax®	n/a	EPS, FEV1; number of days without using rescue medications; number of days without BA symptoms; number of exacerbations; number of AE
22	Rootmensen G. N. et al., 2010 [40]	inhalation technique study, patients selected from randomized trial (n = 156, age above 18 years)	Diskus® Diskhaler® Turbuhaler® Cyclohaler® single-dose PBI DAI DAI + spacer	n/a	number of mistakes in inhalation technique (by steps)

RCT - randomized clinical trial; EPS - expiratory peak speed; FEV1 - forced expiratory volume per 1 sec; h.d. - high dose; e.d. - equivalent dose

Modeling

Due to the lack of long-term data on the compared therapy schemes under the first scenario, the economic evaluation was performed using the probabilistic Markov switching model, which is built in Microsoft Excel and applied to modeling patient switching between different health statuses. Figure 3 presents Markov model structure.

Probabilities of BA state transition for therapy with Symbicort® Turbuhaler® (Table 20 were defined based on the study by Bateman E.D. et al. [18] , as well as the duration of the model cycle, which made 1 week. (Table 2)

Table 2. Probabilities of BA state transition for therapy with Symbicort® Turbuhaler®

BA type	Controlled BA	Partially controlled BA	Uncontrolled BA
Controlled BA	0.73	0.21	0.06
Partially controlled BA	0.10	0.72	0.18
Uncontrolled BA	0.02	0.15	0.83

Probabilities of BA state transition for the scheme of switching to alternative medications were calculated based on the Bateman E. D. et al. [18] study using data from the study by Thomas M. et al. [3].

Because the model provides for time horizon selection, loss of patients in the population should be taken into account. Mortality was assessed based on the statistics of mortality of adults (age 18-90 years) in Russia [6]. Based on the mortality data broken down by age and sex, the weighted average coefficients for each age of patients were calculated in consideration of the duration of 1 cycle of the Markov model. For obvious reasons, this value turned out to be the same for all types of therapy.

Cost analysis

During the next stage of the pharmacoeconomic study, based on the data about the shares of patients with various levels of BA control, data about the rate of using healthcare resources, costs of medications and certain types of medical aid, and also with account of costs associated with temporary disability, the aggregate costs of using the compared medications were calculated.

First, the costs of pharmacotherapy with the compared medications were analyzed. The dosing schedule for maintenance therapy was defined by the Basic Prescribing Information (BPI) for the compared medications [11-17]. For reliever therapy, the exact number of puffs of rescue medications was set based on Sears M. R. et al., 2008 [22] study data and made 0.94 puffs

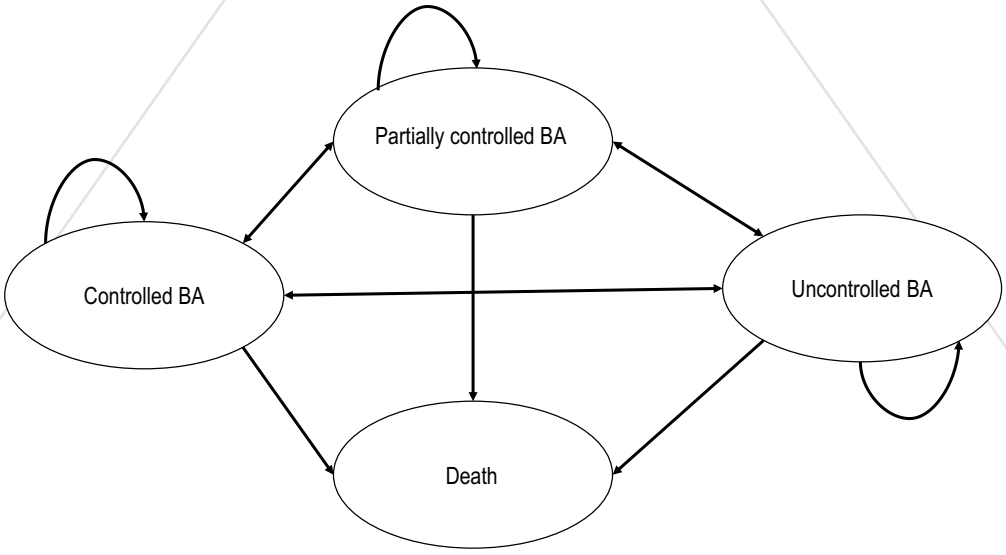


Figure 3. Markov Model Structure, Scenario 1

per day for all Budesonide/Formoterol medications: Symbicort Turbuhaler®, Formisonid-Nativ® and DuoResp Spiromax, irrespective of BA control level. This assumption in favor of alternative medications was made given the lack of other data proving the impact of the specific Budesonide/Formoterol delivery device on the number of doses used as reliever therapy for compensation of asthmatic attacks. The number of Salbutamol doses amounted to 1.09 puffs per day [22] when administered together with Foradil® Combi®, Foster, Seretide® and Seretide® Multidisk®.

To build a reference case for the model, the most common pharmaceutical forms were selected for every medication under the two scenarios on the basis of the data search performed. All Budesonide/Formoterol medications were used in the sole inhalation device mode (Tables 3, 4).

Table 3. Dosing Schedule - Scenario 1

Trade name	Presentation	Number of doses per day			Pack price, RUB	Cost of dose, RUB
		Con-trolled BA	Partially con-trolled BA	Un-con-trolled BA		
Maintenance therapy Line						
Symbicort® Turbuhaler®	160 µg + 4.5 µg, 120 doses	2	4	4	2,198.	18.32
DuoResp Spiromax®	160 µg + 4.5 µg/dose, 120 doses, 1 inhalation device	2	4	4	1,643	13.69
Formi-sonid-Nativ®	160 µg + 4.5 µg/dose, 120 pieces	2	4	4	1,729	14.41
Reliever therapy line						
Symbicort® Turbuhaler®	160 µg + 4.5 µg, 120 doses	0.94	0.94	0.94	2,198	18.32
DuoResp Spiromax®	160 µg + 4.5 µg/dose, 120 doses, 1 inhalation device	0.94	0.94	0.94	1,643	13.69
Formi-sonid-Nativ®	160 µg + 4.5 µg/dose, 120 pieces	0.94	0.94	0.94	1,729	14.41

Table 4. Dosing Schedule - Scenario 2

Trade name	Presentation	Number of doses per day	Pack price, RUB	Cost of dose, RUB
Maintenance therapy Line				
Symbicort® Turbuhaler®	160 µg + 4.5 µg, 120 doses	2	2,198	18.32
Foster®	100 + 6 µg/dose, 120 doses	2	1,900	15.83
Seretide®	25 µg + 125 µg/dose, 120 doses	4	1,126	9.38
Seretide® Multidisk®	50 µg + 250 µg/dose, 60 doses	2	1,205	20.08
Foradil Combi®	set of 200 µg + 12 µg No.60+60	2	959	15.98
Reliever therapy line				
Ventolin	100 µg/dose, 200 doses	1.09	107	0.54
Symbicort® Turbuhaler®	160 µg + 4.5 µg, 120 doses	0.94	2,198.	18.32

Based on the presented Dosing Schedule, the pharmacotherapy costs were calculated in accordance with the prices from the State Registry of Maximum Sale Prices as of December 2016 [8] per year and per patient.

During the next phase, we analyzed the costs associated with using healthcare resources. The frequency and severity of exacerbations depend on the level of BA control. Based on that, we calculated the costs of hospitalization, calling the ambulance and additional visits to the physician. Costs of oral corticosteroids courses were not accounted for due to unavailability of data. The frequency of medical services delivery during exacerbation stage per patient/year depending on the level of BA control was obtained from publication by Demko I.V. [5]:

For Scenario 1, we assumed that the frequency of using the resources for partially controlled BA equals the frequency for uncontrolled BA due to unavailability of additional data. Then, using the rates published by the Federal Compulsory Medical Insurance Fund for Moscow (as of December 2016) [9] covering visits to physician within the outpatient system, calling the ambulance and delivering in-patient care for completed therapy case, and applying the above described frequency of medical services delivery, we received the respective costs for each medication.

After that, we assessed the costs of side effects compensation, the frequency and types of which were described in Basic Prescribing Information (BPI) for the compared medications [11-17] due to unavailability of the respective data in the reviewed studies. Side effects were grouped as follows depending on their frequency in accordance with the World Health Organization's (WHO) classification: very frequent (>1/10); frequent (>1/100, <1/10); infrequent (>1/1000, <1/100); rare (>1/10.000, <1/1000); very rare (<1/10.000); isolated occurrences (frequency cannot be defined). The medical aid rates were calculated based on the respective Standards, clinical recommendations, reference books, rates for completed therapy case or expert opinion, using the rates published by the Federal Compulsory Medical Insurance Fund for Moscow [9].

During the final stage, we analyzed indirect costs of BA therapy based on the data provided by Demko I.V. [5] about the number of temporary disability days for patients with uncontrolled BA (22.8 days), as well as data about average salary in the RF and per capita GDP [7].

Thus, we received the following cost analysis results (see Tables 5 and 6):

Table 5. Results of cost analysis per patient per year for Scenario 1, RUB

Trade name / Type of costs	Symbicort® Turbuhaler®	DuoResp Spiromax®	Formisonid-Nativ®
Pharmacotherapy	23,809	18,851	19,843
Reliever medications	6,256	4,675	4,921
Hospitalization cases	28,087	31,882	31,882
Additional visits to physician	428	484	484
Calling the ambulance	15,761	17,890	17,890
Side effects compensation	652	644	773
Costs associated with temporary disability	42,047	47,729	47,729
Total costs	**117,040**	**122,155**	**123,523**

Table 6. Results of cost analysis per patient per year, Scenario 2, RUB

Trade name / Type of costs	Symbicort® Turbuhaler®	Foster®	Seretide®	Seretide® Multidisk®	Foradil Combi®
Pharmacotherapy	13,374	11,558	13,694	14,660	11,668
Reliever medications	6,286	214	214	214	214
Hospitalization cases	27,691	31,224	31,902	31,902	32,223
Additional visits to physician	423	474	484	484	489
Calling the ambulance	15,538	17,521	17,901	17,901	18,082
Side effects compensation	652	570	1,033	1,024	90
Costs associated with temporary disability	41,455	46,744	47,759	47,759	48,239
Total costs	**105,418**	**108,305**	**112,986**	**113,943**	**111,004**

Based on the obtained results, it is possible to conclude that therapy with Symbicort® Turbuhaler® as the sole inhaler is less costly versus analogous medications (generics), as well as compared to other combinations of ICS/LABA administered together with SABA as reliever therapy. This result is explained by lower direct cost of ambulance, in-patient and out-patient services, as well as by lower indirect costs associated with temporary disability.

Budget impact analysis

Budget impact analysis was the next phase of our study. We took into account the data about therapy duration for patients with BA to assess economic impact on the healthcare system budget in case of choosing therapy with ICS/LABA. The time interval used for our analysis was 1 year for all compared alternatives. It was assumed for the purposes of budget impact analysis calculations that it was possible to choose the number of patients.

We analyzed two hypothetical situations associated with the market share of the compared alternatives for Scenarios 1 and 2. According to the study design, in the current situation all the patients (i.e., 100%) were using Symbicort® Turbuhaler® as the sole inhaler, and in the simulated situation the patients switched to other inhalers with equal distribution of market shares. This calculation allowed for evaluating the budget income of unauthorized switching of patients from Budesonide/Formoterol Turbuhaler® therapy to therapy with other ICS/LABA or to Budesonide/Formoterol therapy delivered by other inhalation devices. The calculation was done for 1,000 patients.

The budget impact analysis resulted in the following values of additional budget expenses presented in Figures 4 and 5 for Scenario 1 and Scenario 2, respectively. In addition, the data received were expressed in the change of frequency of drawing the healthcare system resources.

Therefore, switching of 1,000 patients from Symbicort® Turbuhaler® to its generics/analogues and to other medications of the ICS/LABA group resulted in additional budget expenditures of RUB 3,865,843 and RUB 4,913,273 under Scenario 1 and Scenario 2, respectively - due to the increased number of hospitalization cases by 92 and 120 cases per year (c/y), unplanned visits to physicians by 156 and 203 c/y, calls for ambulance by 316 and 412 c/y, as well as increase in number of temporary disability days by 1,617 and 2,107 c/y, respectively. All the above evidences in favor of the hypothesis underpinning this pharmacoeconomic study: unauthorized switching of patients to cheaper analogues results in higher expenses of the healthcare system due to expensive compensation of the arising exacerbations despite lower costs of pharmacotherapy *per se*.

Conclusions

The pharmacoeconomic analysis of continuation of using Symbicort® Turbuhaler® in the bronchial asthma pharmacotherapy allowed for the following findings:

1. According to the cost analysis results, the provided amounts of direct and indirect costs for one-year therapy with Symbicort® Turbuhaler® as

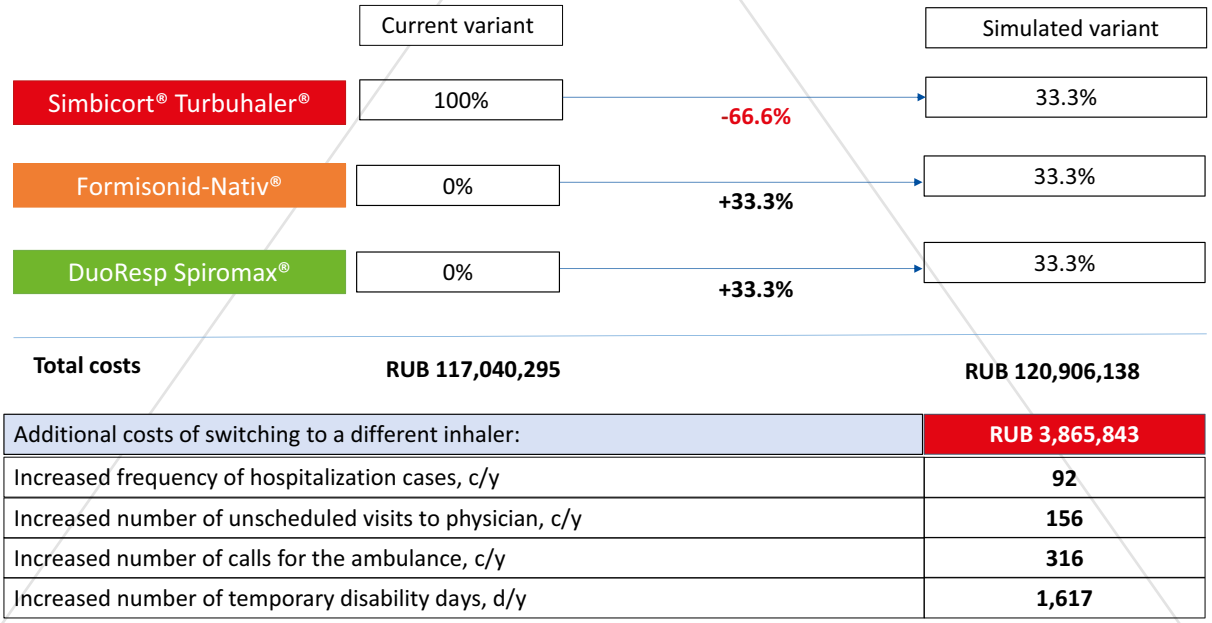
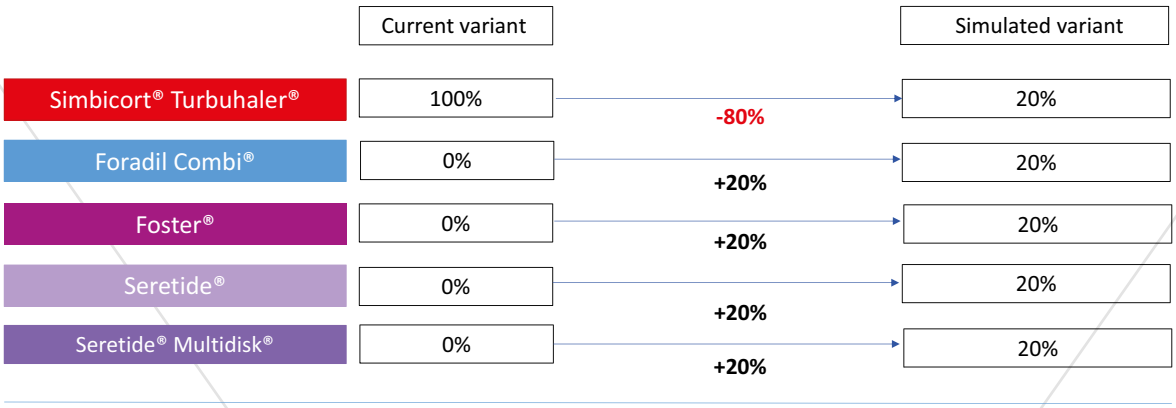


Figure 4. Results of BA Therapy budget impact analysis, Scenario 1



Total costs	**RUB 105,417,972**	**RUB 110,331,246**
Additional costs of switching to a different inhaler:		**RUB 4,913,273**
Increased frequency of hospitalization cases, c/y		**120**
Increased number of unscheduled visits to physician, c/y		**203**
Increased number of calls for the ambulance, c/y		**412**
Increased number of temporary disability days, d/y		**2,107**

Figure 5. Results of BA Therapy budget impact analysis, Scenario 2

the sole inhaler is on average 4.5% lower than the costs of treatment with DuoResp Spiromax®, Formisonid-Nativ®, Foradil Combi®, Foster®, Seretide® and Seretide® Multidisk®.

2. The modeling exercise demonstrated that switching of patients from therapy with Symbicort® Turbuhaler® as the sole inhaler to therapy with DuoResp Spiromax®, Formisonid-Nativ®, Foradil Combi®, Foster®, Seretide® and Seretide® Multidisk® results in 364 additional calls for ambulance, 106 additional hospitalizations, 180 additional visits to out-patient medical centers and 1,862 additional days of temporary disability per 1,000 patients with BA.
3. A budget impact analysis demonstrated that switching of patients from the therapy with budesonis/formoterol Turbuhaler® as the sole inhaler to the therapy with DuoResp Spiromax®, Formisonid-Nativ®, Foradil Combi®, Foster®, Seretide® and Seretide® Multidisk® leads to additional budget expenses of RUB 4 mln (on the average) per 1,000 patients with BA.
4. It is, therefore, clinically and economically reasonable that patients initially receiving Symbicort® Turbuhaler® as a support maintenance therapy to continue therapy using the same medication.

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