AstraZeneca

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A six-month non-interventional prospective study of various controller therapies for moderate persistent and severe persistent asthma in children in real life outpatient clinical practice

Study timelines:	**First subject enrolled:** April 1, 2011
	Last subject completed study: October 2, 2012

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REPORT SYNOPSIS

A six-month non-interventional prospective study of various controller therapies for moderate persistent and severe persistent asthma in children in real life outpatient clinical practice

STUDY TIMELINES

First subject enrolled: April 1, 2011

Last subject completed study: October 2, 2012

STUDY SITES

The present multicenter study was conducted at investigational sites located in Moscow, St. Petersburg, Rostov on Don, Tula, Tver', Samara, Ufa, Novosibirsk, and Chelyabinsk. Ten investigational sites participated in the study. One site (004) was closed due to insufficient patient enrolment.

STUDY OBJECTIVES AND PURPOSES

Primary objective:

To define percentage of children with adequate control of BA symptoms by the end of 6-month observational period (Childhood Asthma Control Test (C-ACT) score > 19).

Secondary objectives:

1) To determine mean number of severe BA exacerbations during 6 months (hospital admissions due to BA exacerbations, cases of daytime hospital treatment without overnight stays and cases of oral administration of glucocorticoids on an out-patient basis for > 3 consecutive days)

2) To determine mean duration of BA exacerbations including hospital admissions, cases of daytime hospital treatment without overnight stays and cases of oral administration of glucocorticoids on an out-patient basis for > 3 consecutive days during the observation period.

3) To determine mean need in short-acting β2-agonists and/or rapidly released methylxanthines per week during the period of observation.

4) To determine % of patients with BA exacerbation associated with an acute respiratory viral infection during the period of observation

5) To determine proportions of patients with various levels of BA symptoms control at the end of observation period.

6) To determine changes of BA symptoms control level based on C-ACT scores at scheduled visits during 6-month observation period.

7) To determine mean pulmonary function changes, as measured based on forced expiratory volume in 1 second (FEV1) and its variability (bronchodilator responsiveness), assessed spirometrically on scheduled study visits (with bronchodilation).

8) To determine health resource utilization (number of unscheduled visits to a physician, number of days in hospital, number of requests for urgent medical aid, number of days in intensive/critical care departments, number of unscheduled visits by a paediatrician at home) during 6-month observation period.

9) To determine patients` adherence to treatment by evaluation of the mean number of days during 28 days period, preceding to a scheduled visit when the patient did not use the recommended dose of ICSs and/or long acting β2-agonists.

10) To determine independent factors associated with BA treatment failure (demographic and baseline patient data, study site).

Safety objectives:

1) To compare incidence of spontaneously reported adverse events (AE) related to maintenance (ICSs and/or long acting β2-agonists) and reliever (short-acting β2-agonists or rapidly released methylxanthines) therapy.

2) To determine incidence of changes in treatment plan or discontinuation of a maintenance therapy due to AE during the observation period.

3) To determine incidence of serious adverse events (SAE) related to maintenance therapy.

4) To determine incidence of any AEs spontaneously reported during the observation period.

STUDY DESIGN

The present study is a multicentre data survey of patients from Russian Federation receiving bronchial asthma (BA) maintenance therapy.

The study was non interventional, i.e. there was no investigational medicinal product.

As a part of the study, each patient performed three scheduled study visits: visit 1 –Day 0 /enrolment and two observational visits (Visit Month 3 and visit Month 6). In case of asthma

exacerbation/worsening, patient could visit the study site for examination to define if it is necessary to change the individual treatment plan or not.

SUBJECT SELECTION CRITERIA

Inclusion criteria

1. Child (male or female) aged 5 to 11 years inclusive.
2. Subject informed consent received for anonymous data collection and usage (must be signed by one of the parents).
3. The child should be included in an out-patient observation program at a medical institution with established BA diagnosis for at least 1 year before enrolment and diagnosed with moderate to severe bronchial asthma at the time of enrolment.
4. The child should have at least one documented severe BA exacerbation (including hospital admissions for BA exacerbations, cases of daytime hospital treatment without overnight stays and cases of oral administration of glucocorticoids on an out-patient basis for > 3 consecutive days).
5. Out-patient receiving maintenance BA therapy with fixed dose combinations (ICSs and long acting β2-agonists) or maintenance therapy with separate administration of ICSs and long acting β2-agonists in stable doses with adequate control of BA symptoms during the previous month, based on the Child Asthma Control Test (score of >19).
6. The child receiving with short-acting β2-agonists (inhaled) or rapidly released methylxanthines (oral) in the doses approved for the respective age as a rescue therapy during the previous month

Exclusion criteria

1. Presence of cystic fibrosis, 1-antitrypsin deficiency or congenital abnormalities of lung development
2. Severe comorbidities affecting the patient's overall performance
3. In the physician's opinion, the patient will not be able to comply with the protocol requirements.
4. Expected specific hyposensibilization within next 6 months.
5. Expected treatment at health resort facilities within next 6 months.
6. Other reasons that in the physician's opinion will prevent adequate assessment of treatment efficacy.

ASSESSMENT CRITERIA

Primary variable: percentage of responders after six months of observation (responder is defined as a subject with C-ACT score > 19 receiving maintenance therapy with inhaled corticosteroid and long acting β2-agonist at Month 6 visit, or the patient who was switched to a lower than step 3 BA treatment during the study participation and was receiving it at Month 6 visit).

Secondary variables

1) Mean number of severe BA exacerbations during 6 months (including hospital admissions for BA exacerbations, cases of daytime hospital treatment without overnight stays and cases of oral administration of glucocorticosteroids) in out-patients for more than 3 consecutive days. The variable will be captured from the patient charts.
2) Mean duration of BA exacerbations (days) including hospital admissions for bronchial asthma exacerbations.
3) Cases of daytime hospital treatment without overnight stay (days).
4) Cases of oral corticosteroid prescriptions for more than 3 consecutive days (mean number of cases) in out-patients.
5) Mean need in short-acting β2-agonists (mean number of inhalations) and/or rapidly released methylxanthines (number of tablets) per week during the 6 months of observation
6) Number (percentage) of patients developed BA exacerbation associated with an acute respiratory viral infection throughout the observation period.
7) Number (percentage) of patients with various degrees of BA symptoms control at the end of 6-month observation period (based on C-ACT scores).
8) Number (percentage) of patients with various levels of BA symptoms control over time (based on C-ACT scores at scheduled visits).
9) FEV1 value and its variability (bronchodilator responsiveness) over time, assessed spirometrically on scheduled visits (with bronchodilation).
10) Mean number of unscheduled visits to a physician throughout the observation period.
11) Mean number of days in hospital throughout the observation period.
12) Mean number of requests for urgent medical aid.
13) Determine the mean number of days in intensive/critical care departments.
14) Mean number of unscheduled visits by a paediatrician at home.
15) Mean height and weight changes during 6 months of observation.
16) Incidence of AEs related to maintenance therapy (ICSs and/or long acting β2-agonists) and urgent relief medications (short-acting β2-agonists or rapidly released methylxanthines) reported throughout the observation period.
17) Mean number of days, during 28-days period preceding the scheduled visit, when patient did not use the recommended dose of inhaled corticosteroid and/or long acting β2-agonist.
18) Incidence of changes in treatment plan or discontinuations of a maintenance therapy due to adverse events during the observation period.
19) Incidence of SAEs related to controller BA treatments.
20) Incidence of all AEs reported throughout the observation period.
21) Independent factors associated with BA treatment failure (demographic and baseline patient data, study site).

PATIENT POPULATION FOR ANALYSIS

Analysis of results was performed in a population of evaluable patients (n=236): receiving step 3 bronchial asthma maintenance therapy including a combination of ICS and long acting β2-agonist, having at least one valid C-ACT evaluation after enrolment and complete data regarding asthma therapy throughout the study and also patients, who discontinued step 3

bronchial asthma maintenance therapy including a combination of ICS and long acting β2-agonist at any time after enrolment according to a known clinical indication, including AE, lack of treatment efficacy and switch to a step 2 bronchial asthma maintenance therapy.

SUMMARY

1. Demographic characteristics

283 patients were enrolled into the study. 4 patients were withdrawn from the study due to their non eligibility according to inclusion/exclusion criteria. Three patients were lost for follow-up after enrolment. 276 subjects completed the study according to the protocol. Significant gaps were discovered in case report forms of 40 patients that forbid the use of these patients for adequate analysis. Eventually, 236 subjects were included into analysis set.

2. Baseline disease characteristics

At the moment of enrolment only 58.4% of subjects had adequately controlled BA according to the C-ACT questionnaire. 81.5% of children had night-time asthma symptoms at least once a week, whereas 97.5% of subjects had day-time symptoms. In 52.7% of study subjects, asthma symptoms affected children's physical activity. Patient distribution according to the treatment prescribed is given in the Table 1.

Table 1. Distribution of subjects by BA combination treatment types

Parameter	Fixed-dose combinations		Non-fixed combination		
	Salm/FP	Bud/Form	BDP + Form	Bud + Form	FP + Form
N	124	51	16	15	30
Mean age, years	8.4±1.9	8.8±1.7	9.3±2.2	9.1±1.8	9.3±1.8
Mean disease duration, years	4.4±2.5	3.5±2.1	3.8±2.3	4.3±1.9	3.8±2.2
Percentage of subjects with severe BA, %	49.5	19.6	1 of 16	2 of 15	16.7
Percentage of subjects with moderate BA, %	60.5	80.4	15 of 16	13 of 15	83.3
Mean dose of ICS calculated as BDP, μg (min-max)	594 (200-1500)	236 (80-640)	227 (100-400)	575 (200-1000)	508 (200-1000)
Mean need in bronchodilators per week	2.4±1.7	1.9±1.3	1.9±1.5	1.7±0.8	2.1±1.7
Mean C-ACT score	20.4±1.69	20,8±2.02	19.4±0.96	21.5±2.36	19.9±1.26
Percentage of subjects with hospitalizations, %	47.6	37.3	4 of 16	4 of 15	26.7

3. Analysis results

Primary objective

Bronchial asthma control

The majority of subjects, who had already achieved adequate disease control at the moment of enrolment, maintained controlled BA throughout the 6-month study period. The highest rate of control maintenance was noted in patient receiving Bud/Form (87.9%). Among patients who were administered non-fixed combinations and Salm/FP, the percentages of subjects who maintained controlled BA throughout the 6 months, were somewhat lower: 85.3% and 80.6%, respectively.

Secondary objectives

1) Throughout the 6-month treatment, BA exacerbations were more rarely observed in the interval between second and third visit, than in the interval between first and second visit (29% and 39.8% of subjects, respectively).

2) No severe exacerbations requiring hospitalization were registered during the study.

3) Mean need in reliever medications per week decreased during the period of observation from 2.18±1.57 to 1.52±2.19 ($p<0.0001$).

4) BA exacerbations associated with a respiratory infection were observed in approximately half of the patients: 52.3% of subjects who received fixed-dose combinations and 52.4% of patients who were administered with non-fixed combinations.

5) Number of patients with controlled BA increased by 42% by the end of observation period.

6) Mean C-ACT score increased from 20.4±1.77 (first visit) to 21.7±2.79 ($p<0.0001$) after three months of observation and to 22.2±3.04 ($p<0.0001$) after six months of observation.

7) Pulmonary function improved, as measured based on forced expiratory volume in 1 second (FEV1) and its variability (bronchodilator responsiveness), assessed spirometrically on scheduled study visits (with bronchodilation).

8) Severe exacerbations required hospitalization or urgent medical aid were not reported during the study.

9) Patient compliance was relatively high in all treatment regimens with some advantage of fixed combinations.

10) No convincing data towards independent factors associated with BA treatment failure (demographic and baseline patient data, study site) were received.

Adverse events

No adverse events related to administration of any asthma medication were registered throughout the study. This data reflect rather low awareness of physicians towards adverse events than real safety profiles of prescribed medications.

4. Summary

Combination treatment with ICS and LABA in children with moderate and severe BA ensures high and stable level of symptoms control, effectively protects patients from severe exacerbations and is well tolerated. The effect of combination treatment advances over the period of more than 6 months. It should be taken into consideration when assessment of combination treatment efficacy is being performed. Administration of fixed-dose combination Bud/Form enables to achieve optimal asthma control level with significantly lower ICS doses, compared to any other combination treatment type. This fact allows us to consider Bud/Form not only an effective combination, but also potentially the most tolerable in children with bronchial asthma.