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# **SYmbicort Given as needed in Mild Asthma (SYGMA study): A Retrospective Subanalysis of the Russian Population**

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## **Abstract**

## **Introduction**

While mild asthma is generally better controlled than more severe disease, patients with mild asthma may experience severe exacerbations. Definite differences between countries in terms of asthma severity and control were described previously. Since SYGMA was a global study, this sub-analysis was conducted in geographic region to investigate potential regional specificities.

## **Methods**

The SYGMA2 trial is double-blind multicenter study involving patients  $\geq 12$  years of age with mild asthma ( $n=4176$ ), eligible for regular treatment with inhaled corticosteroid (ICS). We conducted an open-label descriptive subanalysis of the baseline characteristics of the Russian population ( $n=579$ ) comparing to rest of participants of SYGMA2 trial from other 24 countries. The subanalysis is solely descriptive and will be used for hypothesis generation.

## **Results**

The Russian population of patients with mild asthma hardly differs from the population in other countries in terms of baseline demographic and anthropometric characteristics, smoking status, and duration of asthma. At the study entry few patients from Russia received maintenance therapy with ICS and had symptom control, but the majority was uncontrolled on short-acting bronchodilators, thus the uncontrolled/controlled ratio was 52%/48% vs 45%/55% in other countries. More patients with mild asthma in the Russian group had faced at least one severe exacerbation in the previous year (30.1% vs 20.7%).

## **Conclusions**

The subanalysis revealed a delayed prescription of controller (ICS) therapy and overuse of short-acting bronchodilators in the Russian population with mild asthma. These factors can lead to

insufficient symptom control and higher risk of severe exacerbation in the Russian population with mild asthma.

**Keywords:** Epidemiology, Morbidity and Mortality, Therapy, Treatment, Pharmacotherapy

## **Background**

### ***The epidemiology of mild asthma***

According to the classification offered by the Global Initiative for Asthma (GINA), mild asthma is asthma that is well controlled with Step 1 or Step 2 treatment.<sup>1</sup> Before 2019, Step 1 and 2 treatment included short-acting bronchodilators, as needed, or one of two types of a maintenance medication: either a low-dose inhaled corticosteroid (ICS) or a leukotriene receptor antagonist (LTRA).<sup>1</sup> In the 2019 GINA report an as-needed low-dose combination ICS-formoterol was recommended at step 1 in adults and adolescents as the preferred controller.<sup>1</sup> Mild asthma includes intermittent and mild persistent asthma.<sup>1</sup>

In the comprehensive systematic review by Dusser D et al. (2006)<sup>2</sup> summarizing the state of the knowledge about mild asthma, of the 51,338 references listed since 1997, experts found 154 papers with clinical trial results or meta-analyses on the subject of adult mild asthma and 222 articles on mild asthma in both adults and children. Although a number of epidemiological studies have assessed asthma prevalence in the general population,<sup>3–10</sup> none of them has focused specifically on mild asthma. This approach is complicated due to the absence of a set of standardized epidemiological criteria of mild asthma.<sup>2</sup>

The Asthma Insights and Reality survey (AIR) revealed that, of the 2,803 patients from Western Europe, 63% had mild asthma (44% intermittent and 19% mild persistent).<sup>3</sup> In an international study (Zureik et al., n = 17,089)<sup>4</sup> the prevalence of mild asthma was 50%; the same numbers have been reported in France (n = 4362) by Liard et al.: intermittent asthma – 13%, mild persistent asthma – 27%.<sup>5</sup> Differences in the severity of asthma distributions were found for various age groups: in children under 5 years, 84% had mild asthma (69% – intermittent and 15% – persistent), while in adults over 70 years of age just 62% had it (24% and 38%, respectively).<sup>9</sup>

In their review, Dusser D. et al. conclude that the frequency of mild asthma ranges between 50% and 75%, estimating the worldwide prevalence of mild asthma in the general population at 3.3%.<sup>2</sup> This estimate is confirmed by the results of a recent (2007-2015) population-based cohort study from the UK, where over 60% of all asthma patients had mild disease.<sup>11</sup>

There are no epidemiological studies on mild asthma in the general population in Russia. However, in the multi-center observational study of asthma control in outpatient clinics (n=1000, 12 cities in Russia) the presence of mild asthma was revealed in only 17% of all asthmatics.<sup>12</sup> Symptom control was achieved in 39% of patients with mild asthma, compared to only 21% patients with moderate disease.<sup>12</sup>

### ***Severe exacerbations in mild asthma***

One of the long-term goals of asthma management is minimizing the risk of exacerbations and asthma-related death.<sup>1</sup> While mild asthma is generally better controlled than more severe disease, patients with mild asthma may nevertheless experience exacerbations, including severe and life-threatening ones.<sup>2</sup>

Two large retrospective cohort trials studied exacerbation frequency in patients with asthma. Data were drawn from both US (n=222,817) and UK (n=211,807) databases.<sup>13</sup> Exacerbations were defined as a worsening of asthma requiring an emergency department/hospital admission or oral corticosteroid treatment (which conforms to the definition of a severe exacerbation<sup>1</sup>). Disease severity was assessed per the modified Leidy category (Wells et al., 2012).<sup>14</sup> Twelve-and-a-half percent of patients in the US and 8.4% in the UK experienced  $\geq 1$  exacerbation during a 12-month follow-up period.<sup>13</sup> Mean annual exacerbation rate increased with asthma severity: 0.084 per patient per year in the low Leidy category (mild asthma); 0.159 in low-to-moderate; 0.283 in moderate-to-severe; and 0.547 in the severe category (US data). The same trend was observed in exacerbation frequency (US study data is shown at Figure 1).<sup>13</sup> Thus, severe exacerbations are more common in moderate and severe asthma; nonetheless, approximately 1 out of 10 patients with mild asthma suffers from severe exacerbation within a year's time.

### ***The SYGMA program***

Chronic airway inflammation is known as the main pathogenetic pathway in asthma, and this inflammation persists even in mild asthma<sup>1</sup>, therefore ICS are the cornerstone of asthma treatment across the disease's range of severity.<sup>1</sup> At the same time, adherence to maintenance ICS therapy remains low (ranging between 22% and 63%) and mild asthma is one of the predictors of worse adherence.<sup>15</sup> Suissa S. et al showed using a Canadian cohort of asthma patients (n = 30,569) that irregular use of ICS is associated with a higher risk of hospitalizations<sup>16</sup> and asthma-related death.<sup>17</sup> On the other hand, overreliance on short-acting  $\beta_2$ -agonist (SABA) as a reliever may delay ICS introduction in mild asthma.<sup>3,18</sup>

An alternative symptom-driven regimen of ICS therapy – “anti-inflammatory reliever” or as needed therapy, when budesonide-formoterol (Bud-For) is used on demand, on its own or in conjunction with maintenance therapy, has been introduced into practice.<sup>19</sup> A number of randomized controlled trials studied Bud-For as needed therapy in patients with moderate-to-severe asthma and showed a reduction of severe exacerbation risk compared to the standard maintenance therapy.<sup>19–21</sup>

The low dose ICS-formoterol strategy has been actively discussed as a possible solution for mild asthma.<sup>22</sup> A proof-of-concept study of Bud-For as needed in patients with mild or intermittent asthma has shown promising results.<sup>23</sup> There has emerged a need for larger randomized clinical trials to further explore the Bud-For as needed strategy in patients with mild asthma.<sup>22</sup>

The SYmbicort Given as needed in Mild Asthma (SYGMA) program<sup>18</sup> sought to evaluate the efficacy and safety of as-needed Bud-For in patients with mild asthma and consisted of two 52-week Phase 3 trials: (SYGMA1 (NCT02149199)<sup>24</sup> and SYGMA2 (NCT02224157).<sup>25</sup> The SYGMA trials compared as-needed Bud-For with either maintenance budesonide plus as-needed terbutaline, or as-needed terbutaline alone. The primary endpoints included asthma symptom control and the annual severe exacerbation rate.<sup>18</sup>

In the SYGMA1 trial<sup>24</sup> (full analysis set n=3836) Bud-For as needed was superior to terbutaline as-needed in terms of the mean percentage of weeks of well-controlled asthma per patient 34.4% vs 31.1% (the primary endpoint was met); but was inferior to budesonide maintenance therapy (44.4%). The annual rate of severe exacerbations in as needed Bud/For group (0.07) was lower than in the terbutaline group (0.20) and similar to the budesonide maintenance group (0.09), while the median daily ICS dose in the Bud-For as needed group was much lower (57  $\mu$ g vs 340  $\mu$ g).

The SYGMA2 trial<sup>25</sup> (full analysis set n=4176) also met the primary endpoint: Bud-For as needed was non-inferior to budesonide maintenance therapy in terms of the annualized rate of severe

exacerbation (0.11 vs 0.12). Meanwhile, exposure of ICS In the Bud-For as needed group was approximately one-quarter of that in the budesonide maintenance group.

The issue of mild asthma control and severe exacerbations in these patients is at least as common in Russia as it is in other countries – and of greater import.

Definite differences between countries and regions in terms of asthma severity and control were described In the Asthma Insights and Reality survey (1999-2001)<sup>3</sup> per which 63% patients from Western Europe had mild asthma (44% intermittent and 19% mild persistent), while in Central and Eastern Europe only 41% (22% and 19%, respectively) did.<sup>3</sup> The share of children with lost schooldays because of asthma constituted 43% in Western Europe and 68% in Russia.<sup>3</sup> The use of controller medications in cases of mild asthma in Central and Eastern Europe was less common (in 13% patients with intermittent and 12% with mild persistent asthma) than in Western Europe (in 18% and 30%, respectively).<sup>3</sup>

## Methods

The authors have participated as investigators in the SYGMA 1 and 2 trials, which provided an opportunity to explore recent data about patients with mild asthma in the Russian population. In order to study the peculiarities of mild asthma in Russia (symptom control, real-life therapy, severe exacerbation risk) we sought to conduct a subanalysis of the baseline characteristics of the Russian population in the SYGMA2 trial comparing to the population from other 24 countries\* across the world participated in the SYGMA2 trial. The subanalysis is solely descriptive and will be used for hypothesis generation.

The SYGMA2 trial has been chosen because this study was larger than SYGMA1 (full analysis population n=4176 and n=3836, respectively) and included more patients from Russia, both in absolute terms and as a percentage: SYGMA2 (n=579; 13.9%), SYGMA1 (n=378; 9.9%).<sup>24,25</sup> Finally, the baseline data of the Russian group in the SYGMA2 trial were more complete (there were almost no missing data on the target variables).

We have analyzed the baseline characteristics in the full analysis set of the SYGMA2 trial – randomized patients who received any investigational treatment. The characteristics of the Russian group were compared: a) with the pooled data from other countries (excluding patients from Russia) for percentage variables; b) with the pooled data from all countries (including patients from Russia) for continuous variables.

Only descriptive statistics methods were used; no null hypotheses were tested. Significance of between-group differences was not estimated since we have no access to raw data of other countries. All calculations were performed using Microsoft Office Excel 2005.

footnote

\* Australia, Brazil, Bulgaria, Chile, Colombia, Czech Republic, France, Germany, Hungary, Mexico, New Zealand, Peru, Philippines, Poland, Republic of Korea, Romania, Saudi Arabia, Slovakia, South Africa, Spain, Sweden, Thailand, Ukraine, Vietnam

## Results

The baseline demographic and anthropometric characteristics of groups in the SYGMA2 trial are presented in Table 1.

The Russian population was more homogenous in terms of racial composition (almost exclusively Caucasian) than the population of other countries. Females prevailed in both groups; this predominance was more pronounced among the Russians studied.

The Russian population was slightly older due to a larger proportion of patients  $\geq 50$  years old (43.5% vs 32.6%). The difference in the age median was 5 years. More patients in the Russian group were overweight or obese, with no difference in the Body Mass Index (BMI) median.

There was no difference between the groups in terms of smoking status (Table 1). The vast majority of patients were non-smokers, while the number of pack-years for others was low (4.0).

The duration of asthma was similar in the two groups, both in terms of median time since symptoms first appeared and since the diagnosis was confirmed (Table 2), while maximal asthma duration in the Russian population was higher, probably owing to a higher proportion of older patients.

At enrollment in the SYGMA2 trial, the Russian population included more patients who were uncontrolled on an inhaled short-acting bronchodilator 'as needed' (SABA or/and short-acting muscarinic antagonist – SAMA) than patients who were controlled on mono-maintenance therapy with either a low dose ICS or LTRA, (with ratio 52%/48%), while in other countries saw an inverse of this ratio – 45%/55% (Figure 2).

Pre-study treatment in groups in the SYGMA2 trial is detailed in Table 3. Practically all (>99%) patients in both groups used SABA as-needed to relieve symptoms; the most common SABA was salbutamol (83,4% of patients in Russia and 97.2% in other countries). Russian patients used SAMA more frequently (11.1% vs 1.5%). Most used ipratropium in combination with SABA (63 of 64 SAMA users).

In contrast, controller medications were prescribed in the Russian population more rarely: ICS were taken by less than half of patients, LTRA by just 2%. The most prescribed ICS in the Russian population was beclomethasone, while in other countries it was budesonide.

Baseline lung function parameters were normal or close to normal for the vast majority of patients in both groups (Table 4). The median forced expiratory volume in 1 second (FEV1) before bronchodilator exceeded 80% of the predicted normal, while median post-bronchodilator FEV1 approached 100% of the predicted normal (Table 4). Still, a smaller proportion of patients in the Russian population had pre-bronchodilator  $FEV1 \geq 80\%$  of the predicted normal (59.6% vs 71.7% in other countries) and fewer Russian patients achieved post-bronchodilator  $FEV1 \geq 100\%$  of the predicted normal.

The reversibility of FEV1 after bronchodilator did not differ between groups (Table 4), thus the bronchodilator test was positive in most patients (an increase of FEV1 >12% and >200 mL).

The crucial peculiarity of the Russian population appeared to be the fact that a much higher proportion of patients experienced at least one severe exacerbation in the prior 12 months: 30.1%, compared to 20.7% in other countries (Figure 3).

## Discussion

The retrospective subanalysis of the SYGMA2 clinical trial showed that the Russian population of patients with mild asthma hardly differs from the population in other countries in terms of baseline demographic and anthropometric characteristics, smoking status, and duration of asthma. The

observed differences between the groups in terms of age, sex ratio, and BMI were minimal and did not likely influence symptom control or severe exacerbation risk in a substantial way.

The baseline lung function in the Russian group was slightly worse than in the other population, while being generally within the normal limits for both groups. This observation could be partially explained by differences in racial composition; in fact, the Russian population was almost exclusively Caucasian. The predicted normal values for spirometric parameters in this ethnic group, including FEV1, are higher than they are in other groups.<sup>26,27</sup>

As they joined the study, few patients from Russia had been receiving maintenance therapy (ICS or LTRA) and had symptom control. In fact, the majority of the group was uncontrolled on short-acting bronchodilators (SABA or/and SAMA), thus the uncontrolled/controlled ratio was 52%/48% compared to 45%/55% in other countries.

More patients with mild asthma in the Russian group had faced at least one severe exacerbation in the previous year (30.1% vs 20.7% in other countries).

The present subanalysis revealed the presence of two factors in the Russian population: delayed prescription of controller therapy (mainly ICS) for patients with mild asthma and excessive use of short-acting bronchodilators. The authors posit that these factors can lead to insufficient symptom control and increase the risk of severe exacerbation. This hypothesis is confirmed by the results of large real world evidence studies, showing relationships between SABA overuse and asthma exacerbation risk. Thus, a large proportion (30%) of asthma patients in Sweden had SABA overuse (collected  $\geq 3$  SABA canisters annually).<sup>28</sup> Increased usage of SABA was associated with an increased risk of exacerbations and all-cause mortality.<sup>28</sup> In patients collecting  $\geq 3$  SABA canisters during the baseline year, the hazard ratio for exacerbations was 1.18 and 1.28 on treatment Step 1 and 2, respectively, compared to patients collecting  $\leq 2$  canisters/year.<sup>28</sup> Not only severe asthma (Step 5), but also mild asthma (Step 1, without maintenance ICS therapy) was associated with an increased risk of SABA overuse compared to Step 3 (a 90% and 50% increase in risk, respectively).<sup>28</sup> In the large SABINA program (SABA use IN Asthma) the burden of SABA use was studied in 2006-2017 in more than one million asthmatics  $\geq 12$  years old across 5 European countries (Germany, Italy, Spain, Sweden, the UK).<sup>29</sup> The prevalence of overall SABA overuse ( $\geq 3$  canisters per year) spanned 9-38%.<sup>29</sup> In all countries except the UK, SABA overuse was similar in individuals with mild (9-32%) and moderate-to-severe (8-31%) asthma.<sup>29</sup>

This and similar emerging evidence (including the SYGMA program)<sup>24,25</sup> does not support SABA-only therapy in cases of mild asthma.<sup>30</sup> These novel data have led to significant updates in mild asthma management in the GINA 2019 and 2020 reports, where as-needed low dose combination ICS-formoterol is recommended as the preferred controller for Step 1 in adults and adolescents.<sup>1,30</sup>

The main limitation of this work is its retrospective approach. We cannot exclude the possibility of a systematic bias which may have predisposed patients without controller treatment to be selected for the trial in Russian sites. Nonetheless, the present subanalysis is based on data from a double-blind randomized controlled trial with a large number of participants (>4000) which buttresses the reliability of its conclusions.

When designing this retrospective subanalysis, the authors did not seek to measure or compare the magnitude of differences between Russia and other countries. The main goal of the subanalysis was to receive pilot data on mild asthma in Russia so as to generate hypotheses and plan further studies.

In order to validate the observed data on severe exacerbation risk in Russian patients with mild asthma, and to confirm the relationship between delayed ICS prescription in real practice and a higher risk of severe exacerbations, we believe it is necessary to conduct a purposefully designed prospective clinical trial. This trial should aim to study the characteristics of mild asthma in Russia, while achieving sufficient statistical power and positing the appropriate primary endpoints, namely symptom control and severe exacerbation risk on different therapies.

## Conclusion

The retrospective subanalysis of the SYGMA2 clinical trial showed that the baseline characteristics of Russian population with mild asthma (demographic and anthropometric parameters, smoking status, and duration of asthma) were similar to the other population studied. Lung function (FEV1) in the Russian group was slightly lower compared to other countries.

Before the study fewer patients from Russia received a controller therapy (ICS or LTRA) and had symptom control, yet more Russian patients used only short-acting bronchodilators and were uncontrolled, with the ratio of uncontrolled/controlled at 52%/48% vs 45%/55% in other countries. Also, the Russian population had a substantially larger proportion of patients with at least one severe exacerbation in the previous 12 months (30.1% vs 20.7% in other countries).

The subanalysis of the Russian population with mild asthma revealed late prescriptions of controller (ICS) therapy and excessive use of short-acting bronchodilators, which led to insufficient symptom control and increased the risk of severe exacerbation. It is necessary to more actively implement differential approaches to anti-inflammatory therapy for asthma, starting at Step 1, including ICS-containing regimens – maintenance or/and as-needed.

Declaration of Interest

## Funding

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## Contributors

The study design was conceived by ZRA and ASB. Data analysis was done by SNA and VVA. ZRA drafted the initial manuscript, and all authors reviewed and approved it and subsequent drafts including the final manuscript.

Role of the funding source

The Sponsor was not involved in the subanalysis design, data analysis and interpretation, or writing of the report. The authors had full access to all the data during the subanalysis, and ZRA had final responsibility for the decision to submit the paper for publication.

The views expressed are those of the authors and not necessarily reflect opinions of their institutions or the Sponsor.

Being a principal investigator and national study coordinator in SYGMA1 and SYGMA2 studies ZRA has received investigator and national coordinator fees. ZRA also received speaker/consultancy fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Teva; and research grants from AstraZeneca, GlaxoSmithKline and Novartis, outside the submitted work.

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**Table 1 Demographic and anthropometric parameters of groups in the SYGMA2 trial**

| Variable                       | Russia      | Other countries |
|--------------------------------|-------------|-----------------|
| <b>N, full analysis set*</b>   | 579         | 3597            |
| <b>Race, n (%):</b>            |             |                 |
| Caucasian                      | 575 (99.3%) | 2239 (62.2%)    |
| Asian                          | 4 (0.7%)    | 798 (22.2%)     |
| Other                          | 0           | 560 (15.6%)     |
| <b>Sex, n (%):</b>             |             |                 |
| Male                           | 184 (31.8%) | 1395 (38.8%)    |
| Female                         | 395 (68.2%) | 2202 (61.2%)    |
| <b>Age, years:</b>             |             |                 |
| Median                         | 46.0        | 41.0            |
| Minimum-maximum                | 12-81       | 12-83           |
| <b>Age group, n (%):</b>       |             |                 |
| ≥12–<18 years                  | 58 (10.0%)  | 353 (9.8%)      |
| ≥18–<50 years                  | 269 (46.5%) | 2071 (57.6%)    |
| ≥50–<65 years                  | 186 (32.1%) | 870 (24.2%)     |
| ≥65–<85 years                  | 66 (11.4%)  | 303 (8.4%)      |
| <b>Body Mass Index, kg/m2:</b> |             |                 |
| Median                         | 26.7        | 25.7            |
| Minimum-maximum                | 1653        | 14-59           |
| <25, n (%)                     | 207 (35.8%) | 1652 (45.9%)    |
| ≥25–<30, n (%)                 | 197 (34.0%) | 1151 (32.0%)    |
| ≥30, n (%)                     | 175 (30.2%) | 794 (22.1%)     |
| <b>Smoking status, n (%):</b>  |             |                 |
| Never                          | 508 (87.7%) | 3012 (83.7%)    |
| Current                        | 16 (2.8%)   | 91 (2.5%)       |
| Former                         | 55(9.5%)    | 494 (13.7%)     |
| <b>Number of pack-years:</b>   |             |                 |
| Median                         | 4.0         | 4.0             |
| Minimum–maximum                | 0–9         | 0–13            |

\*who received treatment

**Table 2 Asthma characteristics at enrollment in the SYGMA2 trial**

| Variable                                                            | Russia      | Other countries |
|---------------------------------------------------------------------|-------------|-----------------|
| <b>Time since asthma diagnosis, years:</b>                          |             |                 |
| Median                                                              | 7.6         | 5.8             |
| Minimum-maximum                                                     | 0.4–71.2    | 0.5–47.9        |
| <b>Time since asthma symptoms started, years:</b>                   |             |                 |
| Median                                                              | 10.4        | 9.6             |
| Minimum-maximum                                                     | 0.5–71.2    | 0.6–51.9        |
| <b>Number of severe exacerbations in the last 12 months, n (%):</b> |             |                 |
| 0                                                                   | 405 (69.9%) | 2852 (79.3%)    |
| ≥1                                                                  | 174 (30.1%) | 745 (20.7%)     |
| <b>Pre-study treatment and control, n (%):</b>                      |             |                 |
| Uncontrolled on SABA or/and SAMA                                    | 302 (52.2%) | 1632 (45.4%)    |
| Controlled on ICS or LTRA                                           | 277 (47.8%) | 1965 (54.6%)    |

ICS – inhaled corticosteroid; LTRA – leukotriene receptor antagonist;

SABA – short-acting  $\beta$ 2-agonist; SAMA – short-acting muscarinic antagonist.

**Table 3 Pre-study treatment of groups in the SYGMA2 trial**

| Medications*           | Russia, n | Other countries, n | Russia, % | Other countries, % |
|------------------------|-----------|--------------------|-----------|--------------------|
| <b>ICS:</b>            |           |                    |           |                    |
| No                     | 313       | 1853               | 54.1%     | 51.5%              |
| Yes                    | 266       | 1744               | 45.9%     | 48.5%              |
| <b>LTRA:</b>           |           |                    |           |                    |
| No                     | 568       | 3375               | 98.1%     | 93.8%              |
| Yes                    | 11        | 222                | 1.9%      | 6.2%               |
| <b>SABA as needed:</b> |           |                    |           |                    |
| No                     | 1         | 8                  | 0.2%      | 0.2%               |
| Yes                    | 578       | 3589               | 99.8%     | 99.8%              |
| <b>SAMA:</b>           |           |                    |           |                    |
| No                     | 515       | 3543               | 88.9%     | 98.5%              |
| Yes                    | 64        | 54                 | 11.1%     | 1.5%               |
| <b>SABA and SAMA:</b>  |           |                    |           |                    |
| No                     | 516       | 3551               | 89.1%     | 98.7%              |
| Yes                    | 63        | 46                 | 10.9%     | 1.3%               |
| <b>ICS molecule:</b>   |           |                    |           |                    |
| Budesonide             | 98        | 701                | 16.9%     | 19.5%              |
| Fluticasone            | 23        | 440                | 4.0%      | 12.2%              |
| Beclomethasone         | 130       | 251                | 22.5%     | 7.0%               |
| Ciclesonide            | 2         | 315                | 0.3%      | 8.8%               |
| Other                  | 13        | 37                 | 2.2%      | 1.0%               |

\* Includes treatment taken within 30 days prior to run-in.

ICS – inhaled corticosteroid; LTRA – leukotriene receptor antagonist; SABA – short-acting  $\beta$ 2-agonist; SAMA – short-acting muscarinic antagonist.

**Table 4** Lung function data for groups in the SYGMA2 trial

| Variable*                                               | Russia      | Other countries |
|---------------------------------------------------------|-------------|-----------------|
| <b>FEV1 pre-bronchodilator, % of predicted normal:</b>  |             |                 |
| Median                                                  | 82.2        | 85.1            |
| Minimum–maximum                                         | 60.3–141.5  | 41.6–141.5      |
| <60%, n (%)                                             | 0           | 4 (0.1%)        |
| $\geq 60\%$ – <80%, n (%)                               | 234 (40.4%) | 1010 (28.1%)    |
| $\geq 80\%$ – <100%, n (%)                              | 284 (49.1%) | 2111 (58.7%)    |
| $\geq 100\%$ , n (%)                                    | 61 (10.5%)  | 467 (13.0%)     |
| <b>FEV1 post-bronchodilator, % of predicted normal:</b> |             |                 |
| Median                                                  | 95.0        | 97.0            |
| Minimum–maximum                                         | 76.5–156.5  | 61.2–163.5      |
| <80%, n (%)                                             | 2 (0.3%)    | 35 (1.0%)       |
| $\geq 80\%$ – <100%, n (%)                              | 371 (64.1%) | 2081 (57.9%)    |
| $\geq 100\%$ , n (%)                                    | 205 (35.4%) | 1474 (41.0%)    |
| <b>Reversibility, %:</b>                                |             |                 |
| Median                                                  | 15.4        | 13.7            |
| Minimum–maximum                                         | –9–63       | –20–92          |
| <b>Reversibility, mL:</b>                               |             |                 |
| Median                                                  | 390         | 350             |
| Minimum–maximum                                         | –280–1680   | –480–2510       |

\* At study entry (Visit 2). Missing data are not shown (<0.5%).

FEV1 – forced expiratory volume in 1 second.

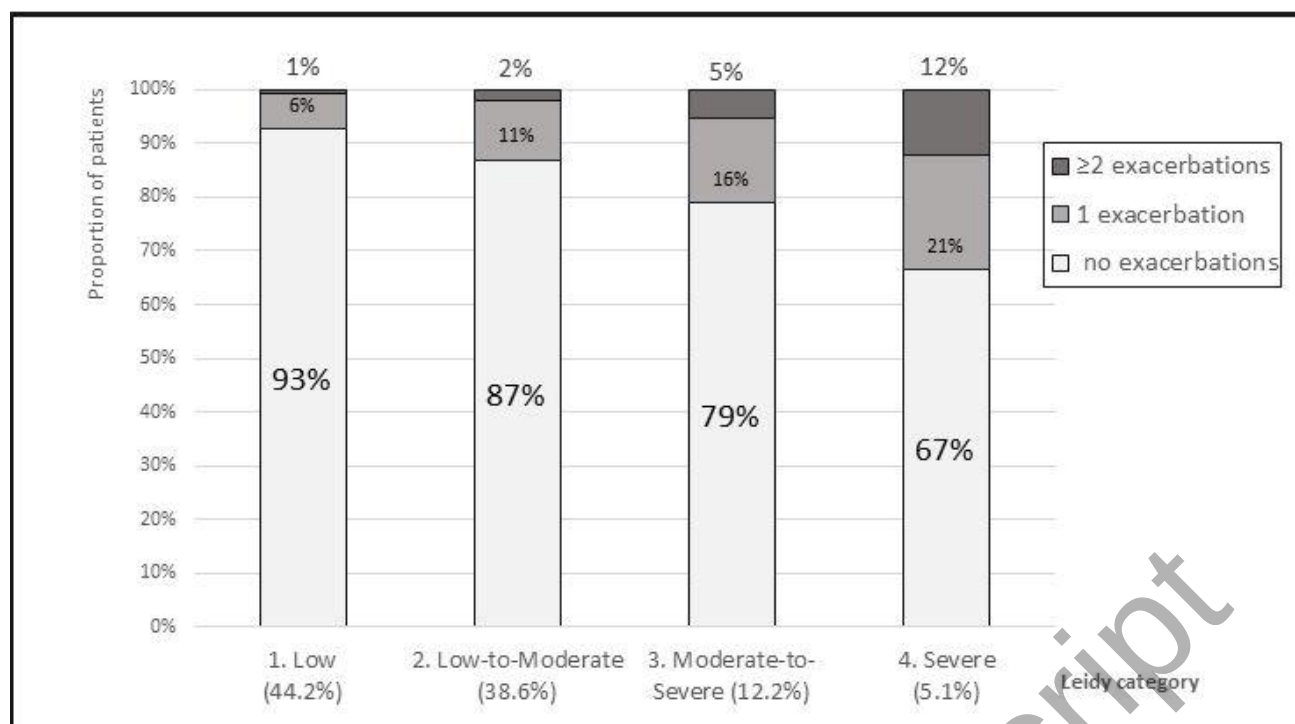


**Figure 1** The frequency of asthma exacerbations during the 12 months of follow-up, by asthma severity (Leidy category) in the US study (n=222,817), modified from <sup>13</sup>

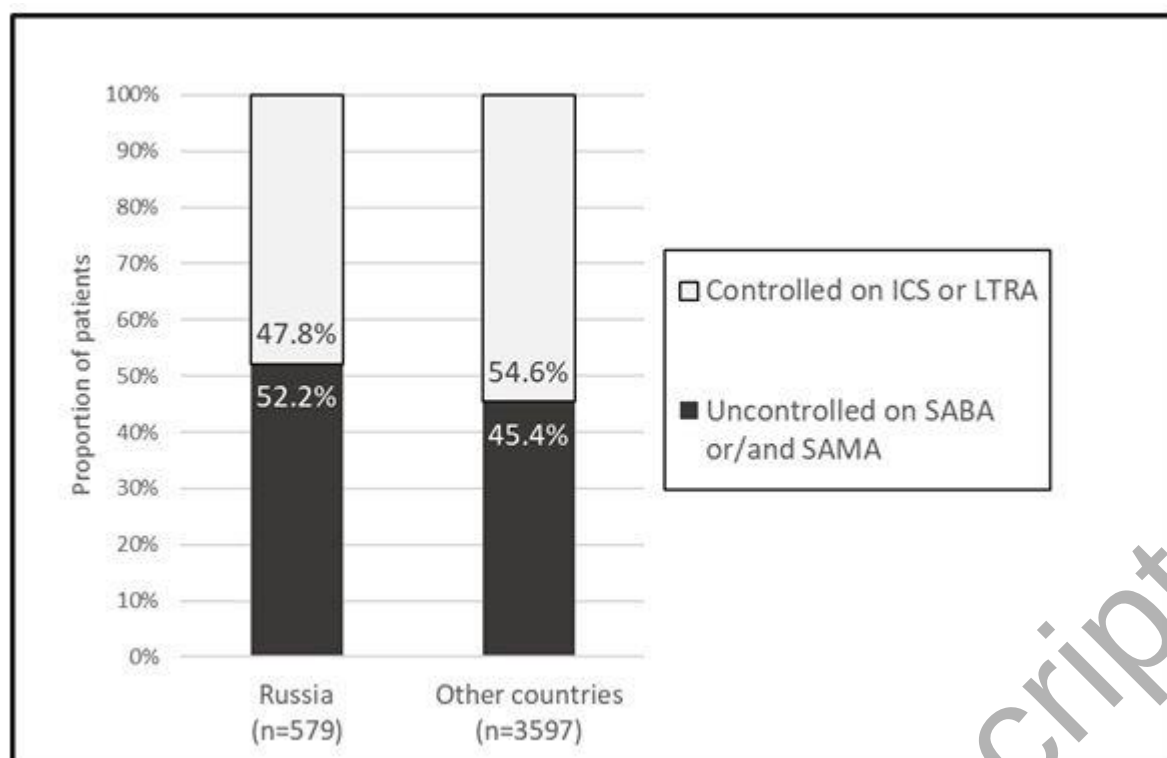


**Figure 2 Pre-study treatment and asthma symptom control**

ICS – inhaled corticosteroid; LTRA – leukotriene receptor antagonist; SABA – short-acting  $\beta$ 2-agonist; SAMA – short-acting muscarinic antagonist.

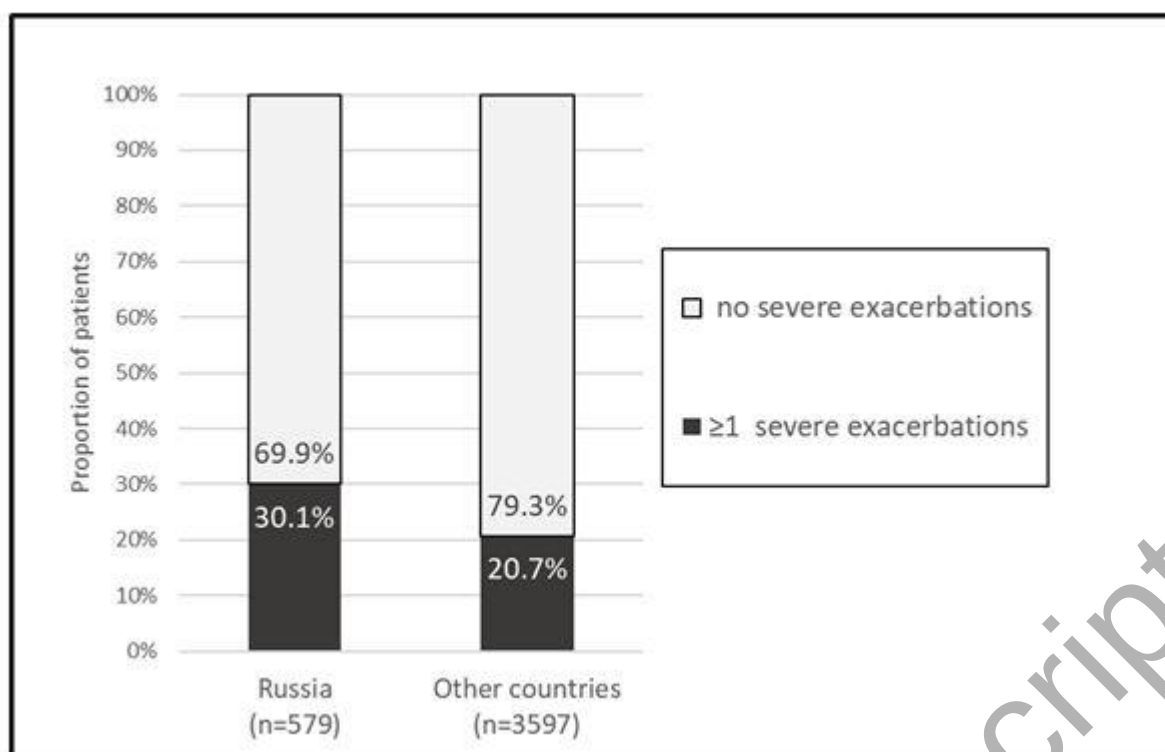


**Figure 3** Number of severe exacerbations in the 12 months prior to enrollment