

Safety of Atrovent[®] CFC-free inhaler: Respiratory events reported from an observational cohort study in England

Vicki Osborne MSc^{1,3}, Deborah Layton PhD^{1,2}, Carole Fogg MSc^{1,2}, Edward Tong PhD¹,
Saad AW Shakir MB ChB LRCP&S FRCP FFPM FISPE MRCPGP^{1,2}

1. Drug Safety Research Unit, Southampton, UK
2. School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK
3. Department of Epidemiology, University of Florida, Gainesville, US

Running title: Safety of Atrovent[®] CFC-free inhaler in England

Corresponding Author:

Prof. Saad AW Shakir
Drug Safety Research Unit
Bursledon Hall
Blundell Lane
Southampton
SO31 1AA
UK

Email: Saad.shakir@dsru.org
Telephone: +44 (0)23 8040 8600
Fax: +44 (0)23 8040 8609

Main text word count: 3119

Contribution statement

Authors had complete access to the study data that support the publication. V.Osborne wrote the manuscript, assisted with data analysis, interpretation of results and conducted literature searching. D.Layton and S.Shakir were involved in the design and implementation of the study, assisted with interpretation of the results and manuscript writing. C.Fogg and E.Tong assisted with data analysis, interpretation of results and manuscript writing.

Acknowledgements

We would like to record our keen appreciation of the co-operation of the general practitioners and numerous other colleagues who have helped in this investigation. We also wish to thank Mr Shayne Freemantle for his assistance with the data analysis. We would also like to thank the NHS Business Services Authority (NHSBSA) in England for their important participation.

1 **Abstract**

2 Objectives: The aim of the study was to identify any unexpected clinical events associated
3 with starting the new CFC-free formulation of Atrovent[®] MDI in general practice in England.

4

5 Methods: An active surveillance cohort study was conducted with a focus on selected clinical
6 events, including respiratory symptoms, in past users of Atrovent[®] CFC MDI ('switchers')
7 and Atrovent[®] naïve users. Incidence density rate ratios (with 99% confidence intervals) for
8 events occurring in the first three months of exposure (risk period-ID₁₋₃) compared to three
9 months prior to starting treatment (reference period-ID_R) were calculated.

10

11 Results: The cohort consisted of 13,211 patients (median age 70 years, 50.1% female; 63.5%
12 prior users of Atrovent[®] CFC MDI ('switchers')). Common respiratory events occurred at
13 higher rates after starting treatment than before for switchers e.g Lower respiratory tract
14 infection (LRTI) [ID₁/ID_R=1.45 (99%CI: 1.17, 1.81)] and worsening asthma [ID₁/ID_R= 1.58
15 (99%CI: 1.00, 2.51)]. Of these events only LRTI was significant for Atrovent[®] naïve patients
16 [ID₁/ID_R= 1.42 (99%CI: 1.04, 1.95)].

17

18 Conclusions: The results of this study suggest effect modification of risk as a result of prior
19 Atrovent[®] CFC MDI use. Overall, Atrovent[®] CFC-free MDI appeared to be reasonably well
20 tolerated in the immediate post-marketing period and the safety profile appeared similar to
21 that of the CFC formulation.

22 **Key Words:** Atrovent; cfc-free; respiratory; cohort; safety

1 **1. Introduction**

2 Atrovent[®] chlorofluorocarbon (CFC)-Free metered dose inhaler (MDI) is a CFC-free
3 formulation of the short-acting anticholinergic bronchodilator, ipratropium bromide.
4 Ipratropium bromide is indicated for “the regular treatment of reversible bronchospasm
5 associated with chronic obstructive pulmonary disease (COPD) and chronic asthma”.¹ The
6 CFC-free formulation of Atrovent[®] MDI was introduced after a decision to phase out CFC
7 propellants due to environmental concerns over the ozone layer.² Hydrofluoroalkane 1,1,1,2-
8 Tetrafluoroethane (HFA 134a) is an alternative propellant for metered dose inhalers (MDI)
9 that has been developed and is used in the CFC-free formulation of Atrovent[®] MDI.²

10
11 An active surveillance cohort study was requested by regulators of the manufacturer with an
12 overall aim to monitor the introduction of the CFC-free formulation in general practice in
13 England, following the switch from the CFC containing formulation of Atrovent[®] MDI. The
14 primary objective of the study was to identify any unexpected clinical events associated with
15 starting the CFC-free formulation of Atrovent[®] MDI, including paradoxical bronchospasm.
16 The secondary objective of the study was to monitor the safety of patients previously and
17 newly exposed (Atrovent[®] naïve) to Atrovent[®] CFC-free MDI in the immediate post
18 marketing period. Of particular interest for both the primary and secondary objectives were
19 respiratory events reported within the first three months after starting treatment, compared to
20 the three months prior to starting treatment.

21
22 To complement the information regarding safety collected from clinical studies and
23 spontaneous reporting schemes, the Drug Safety Research Unit (DSRU) carries out post-
24 marketing surveillance studies of newly marketed drugs with widespread use in primary care
25 in England, using the observational cohort technique known as Modified Prescription-Event

1 Monitoring (M-PEM), which retains all the strengths of the standard observational cohort
2 technique of Prescription-Event Monitoring (PEM)³, but offers more targeted safety
3 surveillance through use of bespoke questionnaires. Such a design was used for this study to
4 monitor the introduction of Atrovent[®] CFC-free inhaler. The main aim of the study was to
5 identify any unexpected clinical events associated with starting the new CFC-free formulation
6 of Atrovent[®] MDI in general practice in England.

7

8 **2. Methods**

9 An M-PEM study was conducted to monitor the safety of Atrovent[®] CFC-free MDI as used in
10 general practice in England. The methods of M-PEM are reported elsewhere.⁵ Briefly, patients
11 were identified by means of data from dispensed National Health Service (NHS)
12 prescriptions, written by General Practitioners (GPs) in England between May 2004 and
13 February 2005. These prescription data were supplied in confidence to the DSRU by the
14 NHS Business Services Authority (NHSBSA).

15

16 At least three months after the first identified prescription was issued for each patient, the
17 prescribing doctor was sent a questionnaire by post. GPs were asked to select the prescribing
18 indication from a list provided on the questionnaire. Where two indications were selected,
19 these were both recorded as the prescribing indication e.g. COPD/Asthma. GPs were also
20 asked questions about when treatment was started and stopped (if applicable), relevant past
21 medical history and any events experienced by the patient in the three months prior to
22 treatment, during treatment and/or in the 30 days after stopping. All indications, relevant past
23 medical history and events reported on questionnaires were coded onto a DSRU database
24 using a hierarchical event dictionary arranged in a system-organ classification, containing
25 higher, lower and doctor summary level terms.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26

2.1 Ethics

This study was conducted in accordance with national and international guidelines⁶⁻⁸. In addition, under Section 251 of the NHS Act 2006, the DSRU have received support from the Ethics and Confidentiality Committee of the National Information Governance Board to gain access to and process patient identifiable information without consent for the purposes of medical research (October 2009).

2.2 Sample size calculation

To find statistically significant differences between number of events occurring prior to and after the first prescription for Atrovent[®] CFC-Free MDI, for events occurring during the pre-exposure period at a frequency of 1/1000 patients and in the post-exposure period at 3/1,000 patients with a power of at least 80%, for a confidence of 99% we needed to recruit at least 12,634 users of Atrovent[®] CFC-Free MDI (EpiInfo V3.5.1, Atlanta, Georgia).

2.3 Data analysis

Summary statistics were produced for patient characteristics (including past medical history), prescribing information and medical event data at aggregate level. Crude odds ratios were calculated for cohort and drug utilisation characteristics comparing naïve users to switchers using STATA v12 (College Station, TX: StataCorp LP). Incidence density rates were calculated for all events reported during treatment for the overall three month post-treatment period (ID₁₋₃). The figures are expressed as ID per 1000 patient-months of treatment. Within this period, two risk periods were defined according to: treatment in the first month after starting Atrovent[®] CFC-Free MDI (ID₁) (“high risk period”), and for the second and third months

1 combined (ID₂₋₃) (“low risk period”) (Figure 1). For individuals who discontinued treatment
2 during the high risk period, a nominal risk period was used equal to the average high risk
3 period observed in the study. If any individual died, a nominal observation period was used
4 based on the average time from event to discharge in other cases.

5
6 IDs were also calculated for the three month period prior to starting Atrovent[®] CFC-Free
7 MDI- the “reference period” (ID_R). Incidence density rate ratios were calculated (99%
8 confidence intervals [CI]) for events, comparing incidence density rates in the high and low
9 risk periods to the reference period. This examined the null hypothesis that the rate for the
10 event was not increasing or decreasing between the two time periods.⁹ The first report of an
11 event for the prior (reference period) and post (3-months after starting treatment) period was
12 included for the incidence density rate ratios, which was an unmatched analysis.

13
14 As IDs for the overall cohort may sometimes mask significant signals in specific risk groups
15 (Atrovent[®] naïve, switchers, asthma patients and COPD patients [not mutually exclusive]),
16 these subgroups had IDs calculated and compared according to strata for respiratory events
17 (ID₁/ID_R, ID₂₋₃/ID_R and ID₁₋₃/ID_R for lower respiratory tract infection, dyspnoea and asthma
18 worse). To minimise confounding, a matched pair analysis was conducted which calculated
19 the risk ratio in the three month observation period pre and post starting Atrovent[®] CFC-Free
20 MDI for *a priori* selected respiratory events at lower level term. Risk ratios (99% CI) were
21 calculated to compare the frequency of selected events in the ‘before’ and ‘after’ periods. Use
22 of a matched analysis improved the power of the statistical test from the unmatched analysis
23 because of the controlling of the matched covariates.

24

3. Results

3.1 Cohort accrual data and characteristics

Dispensed prescriptions were written by 12,771 GPs. Of the 25,706 questionnaires posted to the prescribing GPs, 51.4% (13,211) questionnaires returned contained valid information (16,186 questionnaires returned in total; 63%). The final study cohort comprised 13,211 patients (median age 70 years; 50.1% female). Cohort characteristics are presented in Table 1. The majority of patients in the cohort were switchers from Atrovent[®] CFC inhaler (8,390, 63.5% of cohort) (Table 1).

The most frequently reported indication for prescribing Atrovent[®] CFC-Free MDI was COPD (n=8,408, 63.6% of cohort; 64.4% where indication specified and only in adults), followed by Asthma (n=3161, 23.9% of cohort; 24.2% where indication specified). Further information on the drug utilisation characteristics of the cohort is provided in Table 2.

The season when Atrovent[®] CFC-free inhaler was started was of interest as the winter season is associated with an increased incidence of influenza and respiratory tract infections¹⁰⁻¹², which may result in an increased number of events during this period or may be related to the indication for treatment. The majority of patients (59.6% of cohort) started treatment with Atrovent[®] CFC-free in the autumn and winter months.

3.2 Respiratory events and incidence density ratios for whole cohort

1 The respiratory system organ class had the most events reported overall (4,617, 33.3% of
2 events reported), with the majority of these events occurring post treatment (2,455, 53.2% of
3 respiratory events reported). There were no reports of paradoxical bronchospasm in the study.

4
5 The event with the highest incidence density rate (ID) in the first month of treatment was
6 ‘Lower respiratory tract infection’ ($ID_1=25.25$). The incidence density rate for the total risk
7 period compared to the reference period (ID_{1-3}/ID_R) revealed significantly increased rates for
8 ‘Lower respiratory tract infection’ ($ID_{1-3}/ID_R= 1.28$, 99% CI: 1.12,1.46) and ‘COPD’ ($ID_{1-3}/ID_R= 1.29$, 99% CI: 1.10,1.51) in the total risk period. The corresponding ID ratios for the
9 first month of treatment compared to the reference period (ID_1/ID_R), revealed a significantly
10 increased rate for ‘Lower respiratory tract infection’ in the first month of treatment (‘high risk
11 period’) compared to the reference period ($ID_1/ID_R= 1.42$, 99% CI: 1.19,1.69), and also in the
12 ‘low risk period’ compared to the reference period ($ID_{2-3}/ID_R= 1.20$, 99% CI: 1.03, 1.40),
13 although the point estimate was slightly lower. The rate was also significantly increased in
14 the first month of treatment for ‘COPD’ compared to the reference period ($ID_1/ID_R= 1.52$,
15 99% CI: 1.24,1.86), but there was no significant difference observed for the low risk period
16 ($ID_{2-3}/ID_R= 1.17$, 99% CI: 0.97- 1.40). Of note, the dictionary higher level term ‘COPD’
17 encompasses exacerbations of the disease as well as new diagnoses.

18
19

20 **3.3 Stratified incidence density rate ratios for Atrovent[®] naïve patients and switchers** 21 **from Atrovent[®] CFC MDI**

22

23 Clinical event rates significantly associated with the high risk period in Atrovent[®] naïve
24 patients compared to the reference period included ‘Lower respiratory tract infection’(Figure
25 2) and ‘Respiratory tests’ ($ID_1/ID_R= 4.35$, 99% CI: 1.28, 14.74).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

In the Atrovent[®] CFC MDI switchers subset, an event rate significantly associated with the high risk period compared to the reference period was for the event ‘Lower respiratory tract infection’ (Figure 2). However, unlike the naive subset, this event had a rate which was also significantly higher in the low risk period compared to the reference period. In addition, the rate of ‘COPD’ was significantly associated with both the high and low risk period (ID₁/ID_R= 1.66, 99%CI: 1.31, 2.11; ID₂₋₃/ID_R= 1.26, 99%CI: 1.02, 1.56).

In Atrovent[®] CFC MDI switchers, the rate of ‘Asthma worse’ was associated with starting treatment in the high risk period compared to the reference period, although of borderline significance. The rate of ‘dyspnoea’ was not significantly increased or decreased during the high risk, low risk or total risk periods for both Atrovent[®] naïve and switcher patients.

3.4 Matched analysis results

For all patients in the matched analysis, risk of hospital admissions (RR=1.35, 99% CI: 1.11, 1.65) was significantly greater in the 3 month period after starting than before (Table 3). Also, patients were at greater risk of taking high dose oral steroids (RR=1.21, 99% CI: 1.11-1.32) in the three months post treatment, compared to the three months prior to treatment.

After stratification by prior use of Atrovent[®] CFC MDI, naive users showed a decrease in the risk of dyspnoea after starting treatment with Atrovent[®] CFC-free, compared to the reference period. Atrovent[®] naïve patients had a significantly increased risk of respiratory hospital referrals after starting treatment compared to the reference period. In contrast to Atrovent[®] naive patients, for Atrovent[®] switcher patients, dyspnoea was not shown to be significantly

1 associated with the risk period or the reference period. However, for switchers there was an
2 observation of more frequent use of high dose steroids after starting treatment than prior to
3 starting treatment.

4

5 **3.5 Stratified incidence density rate ratios for COPD and Asthma patients**

6

7 To determine if the indication for treatment had an effect on the incidence density rate ratios,
8 these were further stratified into COPD and asthma patients (Figure 2).

9

10 After stratification by indication, the trend for an increased rate of LRTI after starting
11 treatment was only significantly increased in COPD patients in months 1 and 1-3 of treatment
12 (Figure 2). No other incidence density rates were significantly increased or decreased in
13 COPD and asthma patients.

14

15 **4. Discussion**

16 **4.1 Main study findings**

17

18 Elevated rates of respiratory events in the period after starting treatment in switcher and
19 COPD patients was observed, along with decreased rates of dyspnoea in the period after
20 starting treatment in naïve patients. Since the main aim of the study was to identify any
21 unexpected clinical events associated with starting the new CFC-free formulation of
22 Atrovent® MDI in general practice in England, these results clearly address this aim. Overall,
23 the before and after study design for examining events was successful for estimating the effect
24 of introducing the CFC-free inhaler into England.

25

1 **4.2 Strengths and limitations**

2

3 One of the major strengths of PEM methodology is that it is non interventional and does not
4 influence the prescribing practices of GP's. There are also no exclusion criteria i.e. all patients
5 prescribed and dispensed the study drug are eligible for inclusion.

6

7 However, of the questionnaires sent to GPs (25706), 16186 (63%) were returned. This study
8 did not assess the impact of non-response bias but this response rate is comparable to to
9 response rates reported elsewhere for GP postal surveys²⁵ and higher than the reporting rates
10 of suspected ADRs in the Yellow Card Scheme.²⁶⁻²⁷ Additionally, under reporting of adverse
11 events, including serious and fatal events, is possible in PEM as not all events may be
12 reported to the GP by the patient. Also, as an observational study, it is not possible to
13 estimate the amount of patient compliance with Atrovent[®] CFC-free MDI.

14

15 The delay in submission of this paper was due to several factors: the time required to review
16 questionnaires, code data, perform data cleaning and analysis. There was also a requirement
17 to perform further data analysis, stratifying by indication. However, we feel this paper is still
18 useful for pharmacy practice and that it is important to communicate our findings regarding
19 respiratory events in this patient population. The results still contribute additional information
20 to the current knowledge about this medication.

21

22 **4.3 Event profiles**

23 The majority of patients in the cohort were switchers from Atrovent[®] CFC MDI (8,390,
24 63.5%). It was observed that switchers from Atrovent[®] CFC MDI were more likely to be
25 adults, have an indication of COPD and have moderate/severe disease. Due to the

1 pathological differences between asthma and COPD alone, patients would experience
2 different events¹³⁻¹⁴, but additionally age and disease severity can also create different event
3 profiles¹⁵⁻¹⁷.

4
5 The high risk period was associated with increased reports of both asthma worse and COPD
6 in switchers. The same observation for COPD was also observed for the entire cohort.
7 ‘COPD’ is an indication related higher and lower level term which incorporates the doctor
8 summary terms ‘COPD exacerbation’ and ‘COPD uncontrolled’, among other terms. Since
9 COPD is a progressive disease which can only be controlled and not improved¹⁸, it would be
10 expected for patients to experience these events whilst using Atrovent[®] CFC-free inhaler.
11 ‘Asthma worse’ is an indication related event that indicates a patient’s asthma is not being
12 controlled and is worsening. This indicates that a patient will need to ‘step up’ their therapy¹⁹
13 or change their therapy in an attempt to control their symptoms. Unlike COPD patients,
14 asthma is a disease which can be improved with the right combination of therapy^{13,19}. An
15 explanation for the association with the high risk period for switchers from Atrovent[®] CFC
16 MDI is the seasonality of respiratory tract infections resulting in increased acute
17 exacerbations, and the fact that many patients started Atrovent[®] CFC-free inhaler in the
18 winter months.¹⁰⁻¹²

19
20 For both subsets of patients, the frequency of lower respiratory tract infection was higher after
21 starting treatment than prior. This may be due to calendar time of starting treatment
22 (seasonality) since the majority of patients (59.6%) started treatment with Atrovent[®] CFC-free
23 MDI in the autumn and winter months. The winter season is associated with an increased
24 incidence of influenza and respiratory tract infections^{10-12, 20}, which could provide one
25 explanation of the results of this unmatched analysis. This effect has been seen in another

1 PEM study conducted on the introduction of the CFC-free formulation of Ventolin® Evohaler
2 into the UK population.²¹ Another explanation is protopathic bias. This occurs when the
3 pharmacological agent is prescribed for early manifestation of a condition that has not yet
4 been diagnosed, but which then appears to be the cause of the condition when it is eventually
5 diagnosed.²² Thus, our hypothesis is that both subgroups of patients sought medical advice
6 because of worsening respiratory function, which later turned out to be associated with lower
7 respiratory tract infection, and this diagnosis was recorded at the same time as starting the
8 new CFC-free version of Atrovent®.

9
10 The results of the matched analysis support the observations regarding differences in the event
11 profile between switchers from Atrovent® CFC MDI compared to those who are Atrovent®
12 naive, particularly in terms of severity of indication, ongoing monitoring/referrals and
13 admissions to hospital. The matched analysis produced significant risk ratios for use of high
14 dose oral steroids and hospital admissions for the whole cohort. The significant risk ratio for
15 high dose oral steroids may have been confounded by the increased rate of concomitant lower
16 respiratory tract infections, since patients may require oral steroids to control their disease
17 whilst fighting the infection²³. Due to the elderly population in the cohort, and the high
18 number of patients with COPD, hospital admissions are not unexpected as patients may have
19 experienced exacerbations of COPD requiring admission²⁴, or any other condition relating to
20 age which required admission. Additionally, the high number of admissions may have been
21 related to the season most patients started Atrovent® CFC-free (winter), which is associated
22 with increased hospitalisation due to respiratory infections.^{10-12, 20} Stratified risk estimates of
23 respiratory events such as dyspnoea and respiratory hospital referrals indicate effect
24 modification by past use of Atrovent® CFC MDI. This provides further evidence that when

1 undertaking surveillance studies, it is important to present and discuss issues concerning
2 safety and use separately in these sub-sets.

3

4 The observation of elevated rates of respiratory events in the period after starting treatment in
5 switcher and COPD patients could be suggestive of a period of increased risk after changing
6 treatment regimen in these patients. However, an alternative explanation could be that COPD
7 patients are more likely to experience dyspnoea which cannot improve over time, due to the
8 nature of the disease. In contrast, the cause of dyspnoea in asthma patients can be treated and
9 so improve over time.

10

11 The observation of decreased rates of dyspnoea in the period after starting treatment in naïve
12 patients could be suggestive of a protective effect of Atrovent CFC-free inhaler. A possible
13 explanation for this is that patient's respiratory disease was uncontrolled prior to starting the
14 inhaler, resulting in a higher event rate compared to after starting treatment.

15

16 **5 Conclusion**

17

18 The results of this study suggest possible effect modification of risk as a result of prior
19 Atrovent[®] CFC MDI use and this should be taken into consideration when evaluating the risk
20 benefit profile of new CFC-free formulation inhalers. Overall, Atrovent[®] CFC-free MDI
21 appeared to be reasonably well tolerated in the immediate post-marketing period and the
22 safety profile appeared to be similar to that of the CFC formulation MDI.

23

24

25

26

1 **References**

2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26

1. Boehringer-Ingelheim. Summary of Product Characteristics: Atrovent Inhaler CFC-Free. 2015. UK, Boehringer-Ingelheim Ltd.
2. Taylor J, Kotch A, Rice K, Ghafouri M, Kurland CL et al. Ipratropium bromide hydrofluoroalkane inhalation aerosol is safe and effective in patients with COPD. *Chest* 2001; 120(4): 1253-1262
3. Layton D and Shakir S. Prescription-event Monitoring. In: *Pharmacoepidemiology*. 5th edition. Edited by Strom BL, Kimmel SE, Hennessy S. Chichester,UK: John Wiley & Sons Ltd.; 2012. p. 301-330.
- 4.
5. Layton D, Hazell L, Shakir SA. Modified prescription-event monitoring studies: a tool for pharmacovigilance and risk management. *Drug Saf* 2011;34(12):e1-9.
6. CIOMS/WHO. International Guidelines for Biomedical Research Involving Human Subjects. Geneva; 2002.
7. Royal College of Physicians of London. Guidelines on the practice of Ethical Committees in Medical Research involving Human Subjects. 1996.
8. General Medical Council. Confidentiality: disclosing information for education and training purposes. 2009 [online]. Available at http://www.gmc-uk.org/Confidentiality_disclosing_info_education_2009.pdf_27493403.pdf. Accessed 13 Dec 2016.
9. Stephens MD. The diagnosis of adverse medical events associated with drug treatment. *Adverse Drug React Acute Poisoning Rev* 1987;6(1):1-35.
10. Macfarlane J, Holmes W, Gard P, Macfarlane R, Rose D, et al. Prospective Study of the Incidence, Aetiology and Outcome of Adult Lower Respiratory Tract Illness in the Community. *Thorax* 2001;56:109-14.

- 1 11. Elliot A, Cross K, Fleming D. Acute Respiratory Infections and Winter pressures on
2 Hospital Admissions in England and Wales 1990-2005. *Journal of Public Health*
3 2008;30(1):91-8.
- 4 12. Griffin M, Coffey C, Neuzil K, Mitchel E, Wright P, et al. Winter Viruses: Influenza
5 and Respiratory Syncytial Virus-Related Morbidity in Chronic Lung Disease. *Arch*
6 *Intern Med* 2002 Jun 10;162:1229-36.
- 7 13. Martinez FD, Vercelli D. Asthma. *The Lancet* 2013; 382(9901):1360 - 1372
- 8 14. MacNee William. ABC of Chronic Obstructive Pulmonary Disease: Pathology,
9 pathogenesis, and pathophysiology. *BMJ* 2006; 332 :1202
- 10 15. Raheison C, Girodet P. Epidemiology of COPD. *European Respiratory Review* 2009
11 Dec;18:213-21.
- 12 16. Olin J Tod, Wechsler Michael E. Asthma: pathogenesis and novel drugs for treatment.
13 *BMJ* 2014; 349 :g5517
- 14 17. Wyatt EL, Borland ML, Doyle SK and Geelhoed CG. Metered-dose inhaler ipratropium
15 bromide in moderate acute asthma in children: A single-blinded randomised controlled
16 trial. *J Paediatr Child Health* 2015 Feb;51(2):192-8
- 17 18. Gordon E, Lazarus S. Management of chronic obstructive pulmonary disease: Moving
18 beyond the asthma algorithm. *Journal of Allergy and Clinical Immunology*
19 2009;124(5):873-80.
- 20 19. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British
21 guideline on the management of asthma: A national clinical guideline. 2016.
- 22 20. Garg S, Jain S, Dawood FS, Jhung M, Pérez A, D'Mello T et al. Pneumonia among
23 adults hospitalized with laboratory-confirmed seasonal influenza virus infection-United
24 States, 2005-2008. *BMC Infect Dis* 2015 Aug 26;15:369

- 1 21. Craig-McFeely PM, Wilton LV, Soriano JB, Maier WC, Shakir SA. Prospective
2 observational cohort safety study to monitor the introduction of a non-CFC formulation
3 of salbutamol with HFA134a in England. *Int J Clin Pharmacol Ther* 2003 Feb;41(2):67-
4 76.
- 5 22. Tamim H, et al. Application of lag time into exposure definitions to control for
6 protopathic bias. *Pharmacoepidemiology and drug safety* 2007;16:250-8.
- 7 23. Barnes P, Drazen J, Rennard S, Thomson N. *Asthma and COPD: Basic Mechanisms and*
8 *Clinical Management*. 2 ed. London: Elsevier; 2009.
- 9 24. Miravittles M, Guerrero T, Mayordomo C, Sanchez-Agudo L, Nicolau F, Segu J. Factors
10 Associated with Increased Risk of Exacerbation and Hospital Admission in a Cohort of
11 Ambulatory COPD Patients: A Multiple Logistic Regression Analysis. *Respiration*
12 2000;67(5):495-501.
- 13 25. McAvoy B, Kaner E. General practice postal surveys: a questionnaire too far? *BMJ*
14 1996 Sep 21;313(7059):732-3.
- 15 26. Heeley E, Riley J, Layton D, Wilton L, Shakir S. Prescription-event monitoring and
16 reporting of adverse drug reactions. *Lancet* 2001 Dec 1;358(9296):1872-3.
- 17 27. Martin R, Kapoor K, Wilton L, Mann R. Underreporting of suspected adverse drug
18 reactions to newly marketed ("black triangle") drugs in general practice: observational
19 study. *BMJ* 1998 Jul 11;317(7151):119-20.

20
21
22

1
2
3

Table 1. Cohort characteristics according to prior use of Atrovent® CFC MDI

	Atrovent CFC-free MDI use status			
	Switcher (n=8390)	Naïve user (n=3780)	TOTAL (N=12170) *Not Known =1041	Odds ratio* (95% CI)
Gender				
Male	4106 (67.5%)	1974 (32.5%)	6080	1.14 (1.06, 1.23)
Female ¹	4278 (70.3%)	1804 (29.7%)	6082	
<i>Not Known</i>	6	2	8	
Age				
<=5 yrs	132 (18.4%)	587 (81.6%)	719	11.59 (9.55, 14.06)
6-12 yrs	32 (46.4%)	37 (53.6%)	69	3.01 (1.87, 4.85)
13+ yrs ¹	8226 (72.3%)	3156 (27.7%)	11382	1.00
<i>Not Known</i>	0	0	0	
Oral steroid use either before or during treatment				
Yes	1422 (68.6%)	651 (31.4%)	2073	1.01 (0.91, 1.12)
No ¹	6722 (68.85)	3041 (31.2)	9763	
<i>Not known</i>	246	88	334	
Smoking status ²				
Current or previous smoker	6467 (72.5%)	2449 (27.5%)	8916	0.76 (0.69, 0.84)
Non smoker ¹	1422 (70.9%)	585 (29.2%)	2007	
<i>Not known</i>	337	122	459	
Hospitalised 3 months prior to starting				
Yes	935 (68.5%)	430 (31.5%)	1365	1.02 (0.90, 1.15)
No ¹	7140 (68.9%)	3224 (31.1%)	10364	
<i>Not known</i>	315	126	441	

4
5
6
7
8
9

*Odds ratio of switchers compared to naïve users

¹Characteristics highlighted in bold were used as the baseline for comparison of the odds

²Patients aged 13 years and over only

Switchers are defined as prior users of Atrovent CFC containing MDI, while naïve users have no previous use of Atrovent CFC containing MDI

1 **Table 2. Drug utilisation according to prior use of Atrovent® CFC MDI**

2

	Atrovent CFC-free MDI use status			
	Switcher (n=8390)	naïve user)	TOTAL (N=12170) *Not Known =1041	Odds ratio* (95% CI)
Total puffs at start				
1-3	380 (50.5%)	373 (49.5%)	753	2.50 (2.14, 2.92)
4-7	3197 (66.9%)	1582 (33.1%)	4779	1.26 (1.16, 1.37)
8¹	3737 (71.8%)	1465 (28.2%)	5202	1.00
9+	423 (86.9%)	64 (13.1%)	487	0.39 (0.29, 0.51)
<i>Not Known</i>	653	296	949	
Indication				
COPD¹	5733 (73.2%)	2097 (26.8%)	7830	1.00
Asthma	1875 (65.0%)	1011 (35.0%)	2886	1.47 (1.35, 1.62)
COPD/Asthma	473 (78.2%)	132 (21.8%)	605	0.76 (0.63, 0.93)
COPD/Other	70 (69.3%)	31 (30.7%)	101	1.21 (0.79, 1.85)
Asthma/Other	48 (23.2%)	159 (76.8%)	207	9.06 (6.53, 12.55)
Other	148 (32.5%)	307 (67.5%)	455	5.67 (4.63, 6.94)
<i>Not Known</i>	43	43	86	
GP opinion on severity of disease				
Mild¹	1348 (56.9%)	1023 (43.2%)	2371	1.00
Moderate	4584 (70.4%)	1930 (29.6%)	6514	0.55 (0.50, 0.61)
Severe	2021 (77.6%)	582 (22.4%)	2603	0.38 (0.34, 0.43)
<i>Not Known</i>	437	245	682	

3 *Odds ratio of switchers compared to naïve users

4 ¹Characteristics highlighted in bold were used as the baseline for comparison of the odds

5 Switchers are defined as prior users of Atrovent CFC containing MDI, while naïve users have no previous use of

6 Atrovent CFC containing MDI

1 **Table 3. Matched analysis results for selected events in naïve and switcher patients**

2

Event type	Risk Ratio	Naïve		p-value	Risk Ratio	Switcher		p-value
		99% CI Lower	99% CI Upper			99% CI Lower	99% CI Upper	
Asthma worse	0.95	0.58	1.55	0.776	1.29	0.90	1.83	0.066
Hospital referrals: Respiratory	4.20	1.17	15.13	0.004	1.41	0.69	2.89	0.219
Hospital admissions	1.02	0.71	1.46	0.889	1.68	1.26	2.24	< .001
Dyspnoea	0.60	0.36	1.00	0.010	1.36	0.93	1.98	0.037
High dose oral steroids	1.09	0.90	1.32	0.309	1.28	1.13	1.46	< .001

3 Switchers are defined as prior users of Atrovent CFC containing MDI, while naïve users have no previous use of
 4 Atrovent CFC containing MDI

5

6

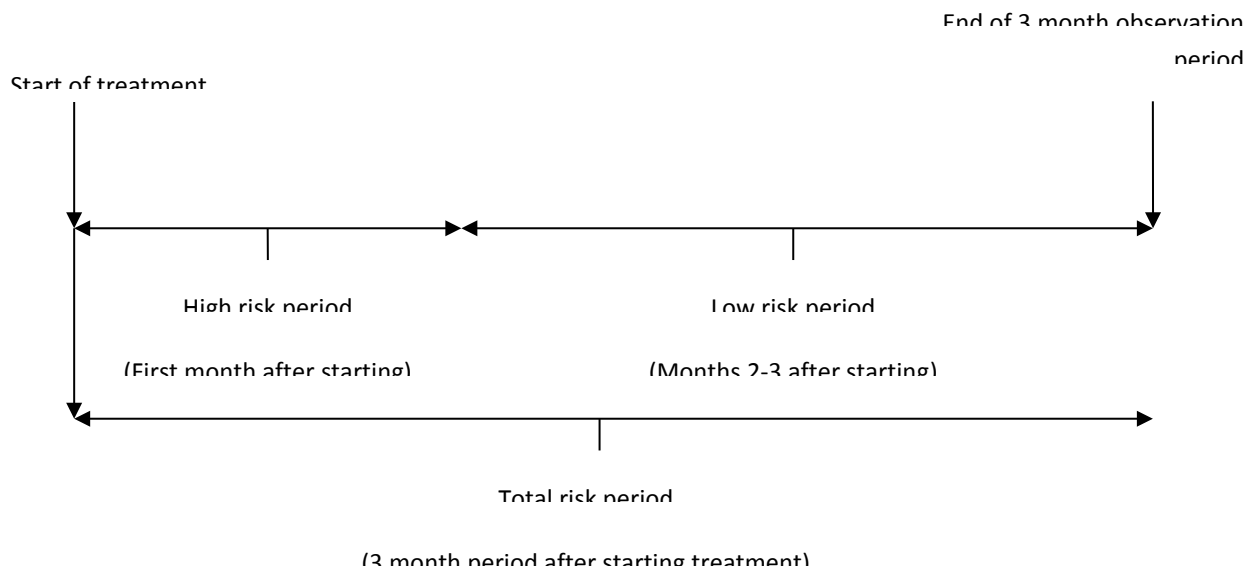
7

8

9 **Figure 1. Treatment periods used in incidence density rate analysis**

10

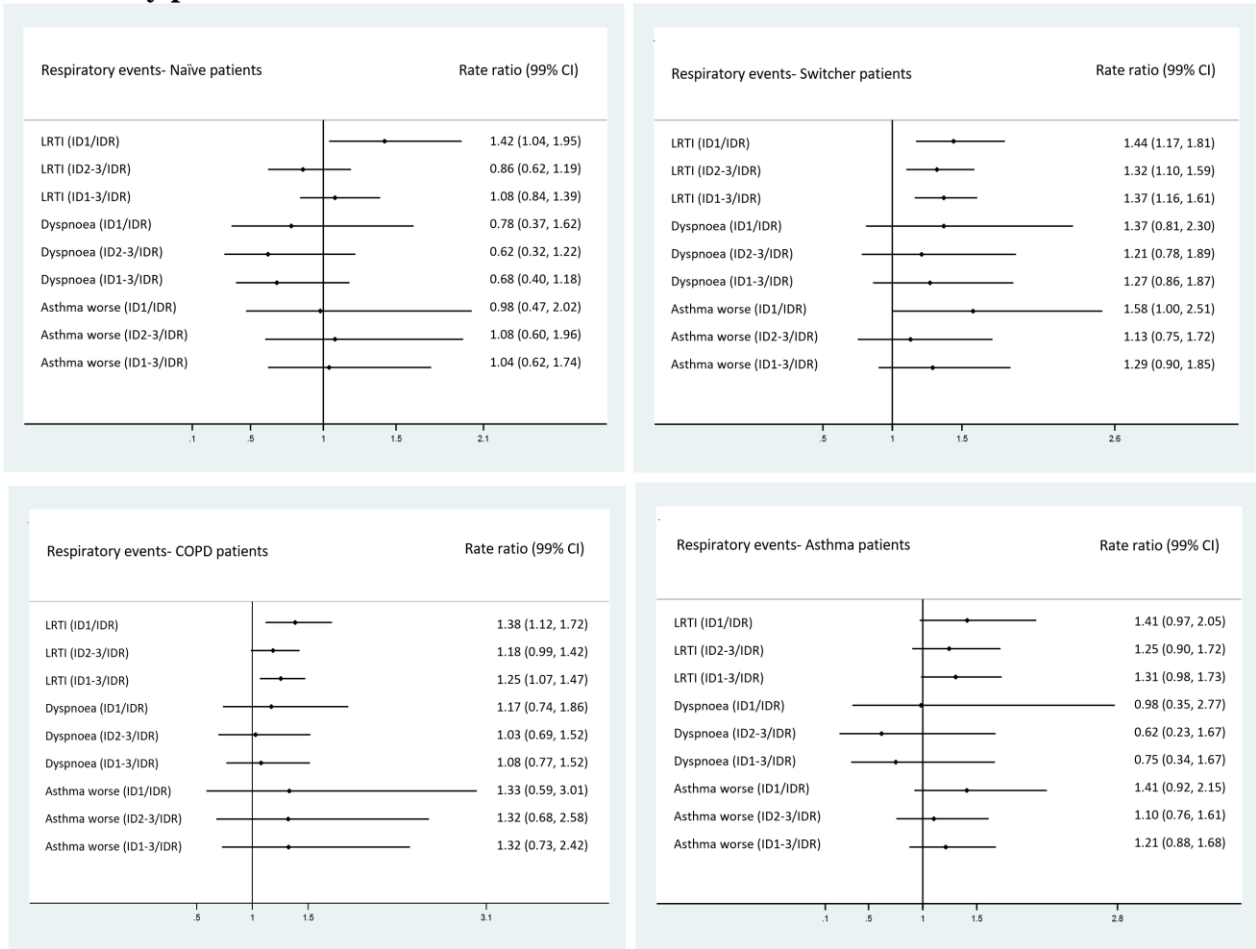
11



12

13

1 **Figure 2. Plot of rate ratios and 99% confidence intervals for respiratory events,**
 2 **stratified by prior Atrovent CFC MDI use and indication**



3

4 LRTI= Lower Respiratory Tract Infection

5

6