

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone
Study No: WEUSRTP1127 / WWE111985
Title: The long-term use of Advair/Seretide and risk of events (incident non-vertebral fracture, glaucoma, and cataracts) among COPD patients in the UK General Research Practice Database
Rationale: Although the long-term use of oral corticosteroids has been associated with increased risk of fracture, cataracts, and glaucoma, the increased risk of these events with long-term use of inhaled corticosteroids (ICS) is less clear due to inconsistent findings across studies. This study fulfils a regulatory post-marketing commitment made at the time of FDA's approval of the ADVAIR sNDA COPD associated with chronic bronchitis indication.
Objectives: The main objective of the study was to conduct three nested case-control studies and obtain measures of the association between the outcomes (non-vertebral fracture, cataracts, and glaucoma) and ADVAIR exposure in a cohort of COPD patients treated in actual clinical practice. The secondary objectives were: to produce fracture, cataract, and glaucoma incidence rates (absolute risk) by categories of exposure defined in the baseline period; to evaluate the association between each outcome and ADVAIR exposure measured according to dose and duration; to evaluate the association between specific non-vertebral fracture sites (hip, upper limb, lower limb, all) and ADVAIR exposure measured according to dose and duration; and to evaluate the association between specific cataract sites (nuclear, cortical, posterior subcapsular) and ADVAIR exposure measured according to dose and duration.
Indication: Chronic Obstructive Pulmonary Disease
Study Investigators/Centers: David P Miller ¹ , Tim J Sampson ¹ , Nada Boudiaf ¹ , Kourtney J Davis ¹ ¹ GlaxoSmithKline R&D, Greenford, UK and Research Triangle Park, USA
Research Methods:
Data Source: The General Practice Research Database (GPRD), managed by the Medicines Control Agency in the United Kingdom, comprises the entire computerized medical records of a sample of general practitioners (GPs) in the England and Wales. All members of the population are registered with a single practice, which centralizes the medical information from GPs, specialist referrals, and hospital attendances. This study is based on data from about a 6% representative sample of the UK population. Data recorded in the GPRD includes demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes. Data are retrieved by means of the Oxford Medical Information Systems (OXMIS) and READ codes.
Study Design: We conducted three case-control studies nested within a cohort of COPD patients in the GPRD to examine each event of interest separately (non-vertebral fracture, cataracts, or glaucoma).

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

Study Population: The study population consisted of a cohort of COPD patients from up-to-standard practices in the UK General Practice Research Database (GPRD) between January 1, 2003 and December 31, 2006. The following inclusion/exclusion criteria were applied: a diagnosis of COPD, age ≥ 45 years at the time of entry, ≥ 1 year between entry into the GPRD (entry in GPRD date) data and the cohort entry date, and no diagnosis of cystic fibrosis or prevalent lung cancer in the 12 month period preceding the initial diagnosis of COPD.

Study Exposures, Outcomes: Exposure to ADVAIR or other ICS (beclomethasone dipropionate, budesonide, fluticasone propionate) was classified in the following ways: 1) Ever use was defined as having at least one prescription of the drug of interest in the one year preceding the index date (date of occurrence of the outcome of interest). 2) Recency of the last exposure prior to the index date was defined as the number of days from the index date within which the last prescription of the drug of interest was prescribed (no use in the last year, within 12 days, 13-25 days, 26-52 days etc). 3) Duration was defined as the sum of the days supplied for each of the prescriptions of interest in the exposure window. Given the possibility of overlapping prescriptions, this number can be greater than 365 days even though only a one year period was evaluated. 4) Number of prescriptions was defined as the sum of prescriptions for each drug of interest in a given exposure window.

We also calculated average daily dose of ADVAIR and other ICS. In the one year preceding the index date, the following time windows were defined for the average daily dose analyses: 0 - 12 months, 0 - 6 months, and 0 - 3 months. By dividing the cumulative dose by the appropriate time window (3, 6, or 12 months), we derived the average daily dose per patient. The following categories of exposure were created to reflect dose ranges in clinical practice: none = No exposure in the time window of interest; low = 1 to 250 FP equivalents; medium = 251 to 500 FP equivalents; high = 501 to 1000 FP equivalents; very high = 1001+ FP equivalents.

Cases of each outcome of interest were defined as incident non-vertebral fractures (diagnosis code), cataracts (procedure or diagnosis code) and glaucomas (procedure or diagnosis code) based on GPRD Medical codes. Controls were patients selected from the risk set, who, at the index date did not have a history of the outcomes of interest and were at risk to become a case. Controls were matched up to 4:1 to cases based on gender, age within two years, general practice, and number of years in the cohort prior to index date (between 2003 and 2006).

We assessed the following variables in the baseline period as potential confounders: age, gender,

Data Analysis Methods: Descriptive tables presenting number and frequency of all variables of interest for each type of analyses were generated. We described the incidence rates (IR) of non-vertebral fractures (NVF), cataracts, and glaucoma in the COPD cohort and in specific strata (see Tables 1, 4, and 7. Conditional logistic regression models were created for matched case and control data to produce adjusted risk (odds ratio [OR]) estimates with 95% confidence intervals (95%CI). Crude and adjusted odds ratios with 95% confidence intervals were estimated for all outcomes. We also used this design to assess a potential dose-response relationship between ADVAIR and the risk of the outcomes of interest.

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

Limitations: 1) Adjustment for potential confounding by indication (disease severity) may have been incomplete. 2) A lack of direct, standardized clinical measurements when utilizing automated databases like the GPRD. Information about other parameters linked to fracture risk, like physical activity, functional status (performance of activities of daily living), community involvement, and assistance with ambulation, are also absent from electronic medical records and could not be adjusted for in multivariate models.

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

Study Results:

Non vertebral fractures:

We identified 1,876 incident non-vertebral fractures (NVF) in the three year study period. Thirty eight percent were upper limb fractures, 22% involved lower limbs, and 21% were hip fractures.

Incidence rates: The incidence rate (IR) per 1000 person years of non vertebral fractures was 19.3 (95%CI: 18.4 – 20.1). The incidence rates were higher with older age, female gender, and lower BMI. Incidence of non vertebral fractures was slightly higher for patients with at least one prescription of ADVAIR (20.2; 95%CI: 18.0, 22.6) versus those with no ICS containing products (17.9; 95%CI: 16.6, 19.3) (Table 1).

Cases and controls: We matched 1,523 of the 1,876 non vertebral fracture cases to 3,749 controls. Thirty-three percent of the cases used ADVAIR in the year prior to the index date compared to 29% of the controls (OR: 1.21; 95%CI: 1.06 – 1.37). Fifty-one percent of cases and controls had a prescription of other ICS. Many factors related to COPD severity were significantly associated with increased risk of NVF (low BMI, oxygen use, COPD-related hospitalizations) (Table2).

Non vertebral fracture risk associated with ADVAIR: Ever use of ADVAIR in the year prior the index date was associated with a slight increase in NVF risk (OR: 1.23; 95% CI: 1.07 – 1.47) (Table 3). Current ADVAIR use (a prescription within 25 days prior to the index date) compared to no prescription in the last year preceding the index date was not associated with increased risk of NVF. Conversely there was a higher NVF risk for patients whose last prescription of ADVAIR was written 26 or more days from the index date compared to no ADVAIR use in the year prior to index date. There was no pattern of increase in risk of NVF with an increase in duration (days supplied) of ADVAIR in the year prior to index date. Similarly, there was no pattern of increase in risk of NVF with increase in the total number of prescriptions of ADVAIR in the year prior to index date. In all of the average daily dose analyses, no pattern of association between increasing level of ADVAIR and increased risk of NVF was observed.

Cataracts:

We identified 2,941 incident cataracts.

Incidence rate: The cataracts incidence rate per 1000 person years was 31.4 (95%CI: 30.3 – 32.6) (Table 4). The incidence rates increased with older age and female gender. Incidence of cataracts was higher for patients with at least one prescription of ADVAIR (35.7; 95%CI: 32.7 – 38.9) versus those with no ICS containing products (27.0; 95%CI: 25.4 – 28.7).

Cases and controls: We matched 2,404 of the 2,941 cataract cases to 5621 controls. Thirty-three percent of the cases used ADVAIR in the year prior to the index date compared to 29% of the controls (OR: 1.19; 95%CI: 1.08, 1.32). Fifty-two percent of cases and 50% controls had a prescription of other ICS in the prior year. Many factors associated with COPD severity were also

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

Glaucoma:

We identified 327 incident glaucomas.

Incidence Rate: The incidence rate per 1000 person years of glaucoma was 3.4 (95%CI: 3.0 - 3.7) (Table 7). The incidence rates were higher for older patients and females. Incidence of glaucoma was similar for patients with at least one prescription of ADVAIR (IR: 3.2; 95%CI: 2.4 – 4.3) versus no ICS containing products (IR: 3.0; 95%CI: 2.5 – 3.6).

Cases and controls: We matched 273 of the 327 glaucoma cases to 703 controls. Twenty-nine percent of the cases used ADVAIR in the year prior to the index date compared to 32% of the controls (OR: 0.84; 95%CI: 0.62 – 1.15). Fifty percent of cases and 48% controls had a prior prescription of ICS (OR: 1.02; 95%CI: 0.77 – 1.36). Some factors associated with COPD severity were associated with a significant increase in glaucoma risk (frequent OCS use, frequent antibiotic use, nebulizer use (Table 8).

Glaucoma risk associated with ADVAIR: None of the different ADVAIR exposure measurements assessed (ever use, days since last prescription received, duration of use, and number of

TABLE 1. Incidence Rates of Non Vertebral Fractures

Description	# of Fractures	Person-Years	Incidence Rate (per 1000 person-years)	95% Confidence Interval
Non-Vertebral Fractures	1876	97478.28	19.25	(18.38, 20.1)
Age_at_Entry				
45-49	45	2598.84	17.32	(12.63, 23.1)
50-54	75	5185.63	14.46	(11.38, 18.1)
55-59	140	9897.42	14.15	(11.9, 16.69)
60-64	186	13545.27	13.73	(11.83, 15.8)
65-69	244	16448.74	14.83	(13.03, 16.8)
70-74	298	17293.74	17.23	(15.33, 19.3)
75-79	347	16558.97	20.96	(18.81, 23.2)

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

80-85	393	12295.44	31.96	(28.88, 35.2)
>=86	148	3654.24	40.50	(34.24, 47.5)
Gender	.	.	.	
Female	1197	45590.57	26.26	(24.79, 27.7)
Male	679	51887.71	13.09	(12.12, 14.1)
BMI				
BMI: Missing	1193	61417.30	19.42	(18.34, 20.5)
BMI: 10 to 18.49	84	2197.29	38.23	(30.49, 47.3)
BMI: 18.50 to 24.99	256	12405.10	20.64	(18.19, 23.3)
BMI: 25 to 29.99	184	11392.53	16.15	(13.9, 18.66)
BMI: 30 to 70	159	10066.06	15.80	(13.44, 18.4)
Smoking_Status				
Non Smoker	197	9220.91	21.36	(18.48, 24.5)
Ex Smoker	472	27076.42	17.43	(15.89, 19.0)
Smoker	480	26229.46	18.30	(16.7, 20.01)
Unknown	727	34951.50	20.80	(19.32, 22.3)
ADVAIR_Use	302	14969.15	20.17	(17.96, 22.5)
ICS_Use	878	43611.62	20.13	(18.82, 21.5)
No ADVAIR and No ICS	696	38897.51	17.89	(16.59, 19.2)

Table 2: Demographics of Non Vertebral Fracture Cases and Controls

Description	Fracture Cases (N=1523)	Fracture Cases (%)	Controls (N=3749)	Controls (%)
Age at Index				
45-49	17	1.12	25	0.67
50-54	32	2.10	73	1.95
55-59	95	6.24	234	6.24
60-64	158	10.37	402	10.72
65-69	209	13.72	574	15.31
70-74	251	16.48	665	17.74
75-79	298	19.57	804	21.44
80-85	352	23.11	786	21.00
>=86	111	7.29	186	5.00
Gender				
Female	965	63.36	2337	62.36
Male	558	36.64	1412	37.64
BMI				
BMI: Missing	843	55.35	1918	51.18
BMI: 10 to 18.49	81	5.32	135	3.60
BMI: 18.50 to 24.99	251	16.48	644	17.18
BMI: 25 to 29.99	204	13.39	550	14.67
BMI: 30 to 70	144	9.46	502	13.39
Smoking Status				

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

Non Smoker	204	13.39	501	13
Ex Smoker	569	37.36	1521	40
Smoker	439	28.82	1047	27
Unknown	311	20.42	680	17
Respiratory Medications				
Advair	502	32.96	1084	28
ICS containing product excluding Advair	783	51.41	1896	50
BDP containing product	570	37.43	1345	35
BUD containing product	178	11.69	449	12
FP Containing product	547	35.92	1225	32
OCS	590	38.74	1489	38
Antibiotic	1062	69.73	2592	67
Nebulizer	223	14.64	485	13
Oxygen	84	5.52	155	4
Other medications				
Calcitonin	1	0.07	1	0
Statin	429	28.17	1165	30
Bisphosphonate	232	15.23	435	11
Anticonvulsant	88	5.78	133	5
HRT	45	2.95	166	4
Comorbidities				
Vertebral Fracture	8	0.53	8	0
Depression	109	7.16	221	5

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

Diabetes	137	9.00	337	8
Rheumatoid Arthritis	12	0.79	28	0
Asthma	205	13.46	489	13
Osteoporosis	44	2.89	89	2
Stroke	26	1.71	54	1
Anemia	62	4.07	108	2
Osteopenia	7	0.46	21	0
Back Pain	239	15.69	465	13
Falls	191	12.54	135	3
Hyperparathyroid	3	0.20	4	0
Dementia	24	1.58	21	0
Hypertension	255	16.74	603	10
Dyslipidemia	58	3.81	174	4
Obesity	145	9.52	507	13
Vitamin D Deficiency	0	0.00	1	0

Table 3. Adjusted Odds Ratios: ADVAIR use in the prior year and risk of Non Vertebral Fracture

ADVAIR	Adjusted OR	95 % CI
<i>Ever use in the last year</i>		
No use in the last year	Reference	
Use in the last year	1.25	(1.07, 1.47)
<i>Last use prior to index date (days)</i>		

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

No use in the last year	Reference	
Last use prior 12 days	1.16	(0.89, 1.5)
Last use prior 13-25 days	1.10	(0.84, 1.46)
Last use prior 26-52 days	1.36	(1.04, 1.77)
Last use prior 53-365 days	1.39	(1.08, 1.78)
<i>Duration of use (days)</i>		
No use in last year	Reference	
1-90	1.28	(1.01, 1.62)
91-180	1.31	(1.01, 1.68)
181-270	1.08	(0.81, 1.46)
>=271	1.33	(1.01, 1.74)
<i>Number of prescriptions</i>		
No prescriptions in last year	Reference	
1-3	1.25	(0.99, 1.58)
4-6	1.37	(1.07, 1.76)
7-9	1.04	(0.77, 1.4)
>=10	1.33	(1.02, 1.75)
<i>Average Daily Dose</i>		
ADVAIR: Average Daily Dose 3 month No Use	1.03	(0.73, 1.44)
ADVAIR: Average Daily Dose 3 month Medium	1.22	(0.84, 1.76)

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

ADVAIR: Average Daily Dose 3 month High	1.22	(0.84, 1.77)
ADVAIR: Average Daily Dose 3 month Very High	1.20	(0.79, 1.84)
ADVAIR: Average Daily Dose 6 month No Use	0.85	(0.65, 1.11)
ADVAIR: Average Daily Dose 6 month Medium	1.01	(0.74, 1.39)
ADVAIR: Average Daily Dose 6 month High	1.15	(0.83, 1.58)
ADVAIR: Average Daily Dose 6 month Very High	1.14	(0.73, 1.76)
ADVAIR: Average Daily Dose 12 month No Use	0.76	(0.62, 0.94)
ADVAIR: Average Daily Dose 12 month Medium	0.90	(0.67, 1.2)
ADVAIR: Average Daily Dose 12 month High	0.92	(0.69, 1.24)
ADVAIR: Average Daily Dose 12 month Very High	1.06	(0.68, 1.66)

All analyses adjusted for COPD Hospitalizations, BMI, Smoking Status, Statin Use, Anticonvulsant Use, HRT Use, Vertebral Fractures, Depression, Diabetes, Anemia, Back Pain, Falls, Dementia, Oxygen Use, Nebulizer Use, Count of Antibiotic prescriptions

TABLE 4. Incidence Rates of Cataracts

Description	# of Cataracts	Person-Years	Incidence Rate (per 1000 person-years)
Cataracts	2941	93567.18	31.43
Age_at_Entry			

GSK Medicine: Salmeterol, Salmeterol+Fluticasone proprionate, fluticasone propionate, beclomethasone

45-49	6	2673.10	2.24
50-54	21	5330.66	3.94
55-59	84	10051.17	8.36
60-64	174	13586.04	12.81
65-69	390	16090.13	24.24
70-74	611	16555.57	36.91
75-79	768	15091.64	50.89
80-85	694	10874.56	63.82
>=86	193	3314.32	58.23
Gender			
Female	1513	43996.39	34.39
Male	1428	49570.80	28.81
BMI			
BMI: Missing	1747	59387.40	29.42
BMI: 10 to 18.49	76	2153.43	35.29
BMI: 18.50 to 24.99	439	11714.50	37.47
BMI: 25 to 29.99	370	10738.97	34.45
BMI: 30 to 70	309	9572.89	32.28
Smoking_Status			
Non Smoker	346	8651.29	39.99
Ex Smoker	943	25558.29	36.90
Smoker	562	25827.54	21.76
Unknown	1090	33530.07	32.51

GSK Medicine: Salmeterol, Salmeterol+Fluticasone proprionate, fluticasone proprionate, beclomethasone

ADVAIR_Use	511	14311.95	35.70
ICS_Use	1411	41524.18	33.98
No ADVAIR and No ICS	1019	37731.06	27.01

Table 5: Demographics of Cataract Cases and Controls

Description	Cataract Cases (N=2404)	Cataract Cases (%)	Controls (N=5621)
Age at Index			
45-49	0	0.00	2
50-54	8	0.33	22
55-59	54	2.25	129
60-64	122	5.07	329
65-69	284	11.81	781
70-74	472	19.63	1220
75-79	697	28.99	1674
80-85	653	27.16	1274
>=86	114	4.74	190
Gender			

GSK Medicine: Salmeterol, Salmeterol+Fluticasone proprionate, fluticasone propionate, beclomethasone

Female	1235	51.37	2793
Male	1169	48.63	2828
BMI			
BMI: Missing	1203	50.04	2958
BMI: 10 to 18.49	82	3.41	185
BMI: 18.50 to 24.99	435	18.09	963
BMI: 25 to 29.99	382	15.89	881
BMI: 30 to 70	302	12.56	634
Smoking Status			
Non Smoker	348	14.48	743
Ex Smoker	1112	46.26	2437
Smoker	493	20.51	1324
Unknown	451	18.76	1117
Respiratory Medications			
ADVAIR	799	33.24	1655
ICS containing product excluding ADVAIR	1260	52.41	2799
BDP containing product	847	35.23	1990
BUD containing product	350	14.56	663
FP Containing product	898	37.35	1864
OCS	1098	45.67	2128
Antibiotic	1681	69.93	3714
Other Medications			
Calcitonin	4	0.17	0

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

Statin	850	35.36	1763
Oxygen	160	6.66	268
Nebulizer	476	19.80	761
Bisphosphonate	369	15.35	594
Anticonvulsant	105	4.37	219
HRT	63	2.62	161
Comorbidities			
Vertebral Fracture	11	0.46	24
Depression	120	4.99	228
Diabetes	350	14.56	538
Rheumatoid Arthritis	11	0.46	40
Asthma	276	11.48	625
Osteoporosis	53	2.20	112
Stroke	38	1.58	74
Anemia	90	3.74	184
Osteopenia	13	0.54	26
Back Pain	307	12.77	627
Falls	137	5.70	247
Hyperparathyroid	4	0.17	4
Dementia	9	0.37	28
Hypertension	364	15.14	946
Dyslipidemia	114	4.74	243
Obesity	306	12.73	639

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

Vitamin D Deficiency

2

0.08

0

Table 6. Adjusted Odds Ratios: ADVAIR use in the prior year and risk of Catar

ADVAIR	Adjusted OR	95 % CI
<i>Ever use in the last year</i>		
No use in the last year	Reference	
Use in the last year	1.10	(0.96, 1.24)
<i>Last use prior to index date (days)</i>		
No use in the last year	Reference	
Last use prior 12 days	1.02	(0.83, 1.27)
Last use prior 13-25 days	1.24	(1.01, 1.51)
Last use prior 26-52 days	1.12	(0.91, 1.38)
Last use prior 53-365 days	1.06	(0.87, 1.30)
<i>Duration of use (days)</i>		
No use in last year	Reference	
1-90	1.06	(0.87, 1.29)
91-180	1.05	(0.87, 1.27)
181-270	1.18	(0.93, 1.49)
>=271	1.20	(0.97, 1.48)

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

<i>Number of prescriptions</i>		
No prescriptions in last year	Reference	
1-3	1.02	(0.84, 1.24)
4-6	1.07	(0.88, 1.3)
7-9	1.20	(0.95, 1.52)
>=10	1.29	(1.05, 1.59)
<i>Average Daily Dose</i>		
ADVAIR: Average Daily Dose 3 month No Use	1.08	(0.81, 1.42)
ADVAIR: Average Daily Dose 3 month Medium	1.16	(0.87, 1.55)
ADVAIR: Average Daily Dose 3 month High	1.07	(0.8, 1.44)
ADVAIR: Average Daily Dose 3 month Very High	1.33	(0.96, 1.85)
ADVAIR: Average Daily Dose 6 month No Use	1.22	(0.97, 1.53)
ADVAIR: Average Daily Dose 6 month Medium	1.20	(0.93, 1.53)
ADVAIR: Average Daily Dose 6 month High	0.91	(0.71, 1.17)
ADVAIR: Average Daily Dose 6 month Very High	1.26	(0.91, 1.76)
ADVAIR: Average Daily Dose 12 month No Use	0.96	(0.81, 1.14)
ADVAIR: Average Daily Dose 12 month Medium	1.07	(0.85, 1.35)
ADVAIR: Average Daily Dose 12 month High	1.17	(0.92, 1.48)
ADVAIR: Average Daily Dose 12 month Very High	1.20	(0.87, 1.66)

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

All analyses adjusted for COPD Hospitalizations, BMI, Smoking Status, Statin Use, Anticonvulsant Use, HRT Use, Vertebral Fractures, Depression, Diabetes, Anemia, Back Pain, Falls, Dementia, Oxygen Use, Nebulizer Use, Count of Antibiotic prescriptions

TABLE 7. Incidence Rates of Glaucoma

Description	# of Glaucoma	Person-Years	Incidence Rate (per 1000 person- years)	95% Confidence Interval
Glaucoma	327	97341.25	3.36	(3.01, 3.74)
Age_at_Entry				
45-49	2	2656.24	0.75	(0.08, 2.72)
50-54	7	5341.19	1.31	(0.53, 2.7)
55-59	12	10088.00	1.19	(0.61, 2.08)
60-64	34	13761.12	2.47	(1.71, 3.45)
65-69	54	16487.25	3.28	(2.46, 4.27)
70-74	71	17241.95	4.12	(3.22, 5.19)
75-79	73	16268.89	4.49	(3.52, 5.64)
80-85	55	12010.52	4.58	(3.45, 5.96)
>=86	19	3486.10	5.45	(3.28, 8.51)
Gender				
Female	171	46272.32	3.70	(3.16, 4.29)
Male	156	51068.93	3.05	(2.59, 3.57)
BMI				
BMI: Missing	217	61567.58	3.52	(3.07, 4.03)

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

BMI: 10 to 18.49	4	2241.49	1.78	(0.48, 4.57)
BMI: 18.50 to 24.99	46	12355.36	3.72	(2.73, 4.97)
BMI: 25 to 29.99	34	11231.91	3.03	(2.1, 4.23)
BMI: 30 to 70	26	9944.91	2.61	(1.71, 3.83)
Smoking_Status				
Non Smoker	29	9057.02	3.20	(2.14, 4.6)
Ex Smoker	91	26775.50	3.40	(2.74, 4.17)
Smoker	73	26504.11	2.75	(2.16, 3.46)
Unknown	134	35004.63	3.83	(3.21, 4.53)
ADVAIR_Use	48	14957.31	3.21	(2.37, 4.25)
ICS_Use	162	43596.91	3.72	(3.17, 4.33)
No ADVAIR and No ICS	117	38787.03	3.02	(2.49, 3.62)

Table 8: Demographics of Glaucoma Cases and Controls

Description	Glaucoma Cases (N=273)	Glaucoma Cases (%)	Controls (N=703)	Controls (%)
Age at Index				
50-54	3	1.10	8	1.14
55-59	9	3.30	20	2.84

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

60-64	24	8.79	54	7.68
65-69	44	16.12	126	17.92
70-74	61	22.34	159	22.62
75-79	66	24.18	179	25.46
80-85	54	19.78	138	19.63
>=86	12	4.40	19	2.70
Gender				
Female	143	52.38	357	50.78
Male	130	47.62	346	49.22
BMI				
BMI: Missing	138	50.55	366	52.06
BMI: 10 to 18.49	4	1.47	23	3.27
BMI: 18.50 to 24.99	56	20.51	111	15.79
BMI: 25 to 29.99	39	14.29	109	15.50
BMI: 30 to 70	36	13.19	94	13.37
Smoking Status				
Non Smoker	31	11.36	91	12.94
Ex Smoker	120	43.96	292	41.54
Smoker	69	25.27	186	26.46
Unknown	53	19.41	134	19.06
Respiratory Medications				
ADVAIR	78	28.57	226	32.15
ICS containing product excluding ADVAIR	136	49.82	338	48.08

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

BDP containing product	90	32.97	223	31.72
BUD containing product	43	15.75	95	13.51
FP Containing product	88	32.23	253	35.99
OCS	119	43.59	264	37.55
Antibiotic	190	69.60	458	65.15
Oxygen	15	5.49	45	6.40
Nebulizer	51	18.68	92	13.09
Other Medications				
Statin	76	27.84	210	29.87
Bisphosphonate	41	15.02	76	10.81
Anticonvulsant	13	4.76	27	3.84
HRT	8	2.93	18	2.56
Comorbidities				
Vertebral Fracture	2	0.73	3	0.43
Depression	12	4.40	38	5.41
Diabetes	23	8.42	76	10.81
Rheumatoid Arthritis	0	0.00	5	0.71
Asthma	35	12.82	75	10.67
Osteoporosis	7	2.56	11	1.56
Stroke	4	1.47	10	1.42
Anemia	5	1.83	20	2.84
Osteopenia	1	0.37	5	0.71
Back Pain	40	14.65	86	12.23

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

Falls	14	5.13	31	4.41
Hyperparathyroid	0	0.00	1	0.14
Dementia	2	0.73	7	1.00
Hypertension	47	17.22	115	16.36
Dyslipidemia	15	5.49	20	2.84
Obesity	36	13.19	95	13.51

Table 9. Adjusted Odds Ratios: ADVAIR use in the prior year and risk of Glaucoma

ADVAIR	Adjusted OR	95 % CI
<i>Ever use in the last year</i>		
No use in the last year	Reference	
Use in the last year	0.68	(0.45, 1.01)
<i>Last use prior to index date (days)</i>		
No use in the last year	Reference	
Last use prior 12 days	1.00	(0.53, 1.89)
Last use prior 13-25 days	0.67	(0.34, 1.3)
Last use prior 26-52 days	0.55	(0.28, 1.09)
Last use prior 53-365 days	0.81	(0.44, 1.52)
<i>Duration of use (days)</i>		
No use in last year	Reference	
1-90	1.02	(0.54, 1.9)
91-180	0.50	(0.26, 0.96)

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

181-270	0.52	(0.25, 1.08)
>=271	0.75	(0.42, 1.34)
<i>Number of prescriptions</i>		
No prescriptions in last year	Reference	
1-3	1.01	(0.54, 1.89)
4-6	0.49	(0.26, 0.93)
7-9	0.50	(0.24, 1.03)
>=10	0.72	(0.39, 1.3)
<i>Average Daily Dose</i>		
ADVAIR: Average Daily Dose 3 month No Use	1.22	(0.52, 2.85)
ADVAIR: Average Daily Dose 3 month Medium	0.96	(0.41, 2.25)
ADVAIR: Average Daily Dose 3 month High	0.80	(0.33, 1.95)
ADVAIR: Average Daily Dose 3 month Very High	1.25	(0.44, 3.56)
<i>Average Daily Dose 6 month</i>		
ADVAIR: Average Daily Dose 6 month No Use	2.50	(1.14, 5.47)
ADVAIR: Average Daily Dose 6 month Medium	0.70	(0.3, 1.63)
ADVAIR: Average Daily Dose 6 month High	1.14	(0.53, 2.45)
ADVAIR: Average Daily Dose 6 month Very High	0.87	(0.28, 2.65)
<i>Average Daily Dose 12 month</i>		
ADVAIR: Average Daily Dose 12 month No Use	1.47	(0.85, 2.54)
ADVAIR: Average Daily Dose 12 month Medium	0.99	(0.47, 2.08)

GSK Medicine: Salmeterol, Salmeterol+Fluticasone propionate, fluticasone propionate, beclomethasone

ADVAIR: Average Daily Dose 12 month High	0.96	(0.46, 1.99)
------------------------------------------	------	--------------

ADVAIR: Average Daily Dose 12 month Very High	1.03	(0.37, 2.81)
-----------------------------------------------	------	--------------

All analyses adjusted for COPD Hospitalizations, BMI, Smoking Status, Statin Use, Anticonvulsant Use, HRT Use, Vertebral Fractures, Depression, Diabetes, Anemia, Back Pain, Falls, Dementia, Oxygen Use, Nebulizer Use, Count of Antibiotic prescriptions

Conclusion: In these nested case control analyses of a large, population-based COPD cohort of 53,191 patients from the UK, we did not observe an association between ADVAIR or other ICS exposures in the prior year and increases in risk of non vertebral fractures, cataracts, or glaucoma. We also did not detect a dose response relationship between average daily dose exposure to ADVAIR or other ICS and increased risk of non vertebral fractures, cataracts, or glaucoma.