The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: Inhaled Corticosteroid (ICS-)-containing Medications as a class were examined in this study. Individual medications were not examined in the study. Medications included: Salmeterol/Fluticasone Propionate and Fluticasone Propionate.

Study Number:e-track: WWE116952; protocol WEUSKOP6416

Title: WEUSKOP6416: Evaluating pneumonia events in patients with Chronic Obstructive Pulmonary Disease (COPD) to inform risk minimization: A Retrospective Observational Study

Rationale: Based on the increased risk of severe pneumonia observed in subjects randomized to Fluticasone furoate / vilanteral (FF/VI), GSK sought to gain a better understanding of the rates and risk factors for severe pneumonia in patients with COPD using retrospective observational studies of the class of inhaled corticosteroid (ICS)-containing medications. The results may be used to identify patients at greater risk of pneumonia requiring hospitalization and may identify where risk minimization and/or medical recommendations may be appropriate to prevent pneumonia or improve pneumonia treatment leading to reduced morbidity and mortality.

Study Period: Final Protocol 27-JUN-2012; Final Study Report-2-MAY-2013

Objectives: The overall objectives of this retrospective observational COPD cohort study were:

- To estimate the magnitude of association between risk factors and pneumonia requiring hospitalization, including ICS-containing medications
- To evaluate if ICS-containing medications modify the effect of risk factors for severe pneumonia (i.e. evaluate statistical interaction between ICS × other risk factors)
- To evaluate any differences in clinical characteristics between subjects who develop pneumonia or severe pneumonia vs. those who do not develop pneumonia in the one year period following new user cohort entry

Indication: Chronic obstructive pulmonary disease (COPD)

Study Investigators/Centers: GSK-conducted database study

Data Source: Clinical Practice Research Datalink's General Practitioner OnLine Database (CPRD-GOLD), with linked Hospital Episode Statistics (HES) and Vital Statistics

Study Design: This was a retrospective observational study in the United Kingdom useing linked primary and secondary care data with vital statistics.

Study Population: Subjects were required to be new users of of long-acting bronchodilator medications (LABD) or ICS-containing medications from January 2002-December 2010, 45 years of age or older, have one year or more of data prior to cohort entry for assessment of subject characteristics, and have the ability to link to Hospital Episode Statistics. Subjects had at least one prescription for LABD, including long-acting beta-agonists (LABA) and long-acting anti-muscarinics (LAMA), or ICS-containing medicine from January 2002 (the earliest use) until December 2010 preceded by a year of no use of either medicine.Subjects with medical conditions potentially confounding the natural course of COPD were excluded (e.g., pulmonary fibrosis, bronchiectasis).

Study Exposures, Outcomes:

Exposures: The primary exposure of interest was ICS, evaluated in a new user cohort of ICS-containing medications. The comparator exposure group of interest was LABD. To account for poor adherence to respiratory medications, subjects were classified as exposed to study medication for the duration of prescribed therapy plus 60 days. Therefore, in the case of a single inhaler (30-days supplied), subjects were allowed for gaps of up to 90 days between prescriptions. To identify a study population of persistent users, we restricted to subjects on treatment for ≥ 6 months.

To examine a potential dose-response relationship with ICS-containing medications, the strength of the prescribed ICS medication on the Cohort Entry Date was categorized into equipotent doses of low, medium, and high-dose ICS based on classification from the Global Initiative for Asthma [estimated equipotent daily doses to beclomethasone dipropinate CFC (BDP) low (200-500 µg), medium (>500-1000 µg), high (>1000-2000 µg)].

Outcomes: Initially, our primary definitions of pneumonia was severe pneumonia, where the subject was hospitalized

for pneumonia or died (for any reason) during their pneumonia episode. As a secondary outcome, any pneumonia (regardless of if it was recorded in primary care or HES) was examined. As 90% of pneumonia episodes resulted in hospitalization where pneumonia was listed as a primary or secondary cause during the hospitalization, additional post hoc analyses to assess sensitivity were added. Four pneumonia definitions (sensitive and specific) were therefore used in this study:

- Overall pneumonia: pneumonia regardless where it was recorded in the subject record, primary care or HES
- Severe pneumonia: pneumonia resulting in a hospitalization or death
- Hospitalized pneumonia: pneumonia resulting in hospitalization where pneumonia was listed as the primary cause for any episode of care during a hospitalization
- Hospitalized with pneumonia on the first episode: pneumonia resulting in hospitalization where pneumonia was listed as the primary cause for the first episode of care during a hospitalization

Data Analysis Methods: This was a retrospective observational study in the United Kingdom using linked primary and secondary care data with vital statistics. Pneumonia and pneumonia hospitalization events in subjects with COPD were compared in new users defined as an initial prescription of ICS-containing medications (n=11,555; ICS, ICS/LABA combination) and inhaled LABD monotherapies (n=6,492; LABA, LAMA) using Cox models (hazard ratios [HR] and 95% confidence intervals [CI]) and propensity scores with inverse proportional treatment weighting (IPTW) to control for confounding. New users were censored at earliest of: pneumonia event, death, switching/stopping treatment, or end of study period. Sensitive and specific pneumonia outcomes were examined including any pneumonia and severe pneumonia resulting in hospitalization or death during the episode. Hospitalized pneumonia was examined further, as primary cause on any episode within a hospitalization and as a primary cause on the first episode within a hospitalization.

Limitations: There are known limitations of non-randomized database analyses of medication safety, including the potential for confounding by severity. ICS-containing medications may have been dispensed to subjects who have more severe COPD or those at higher risk for exacerbation than subjects who are receiving long-acting bronchodilators alone per treatment guidelines. In this study, we adjusted for disease severity in the year prior to initiation using propensity scores, including adjustments for several confounders relating to the assignment to treatment (e.g., lung function, exacerbation history, pneumonia history, smoking status, and rescue medication use). Co-morbidities were also accounted for in the propensity score analysis using the entire subject record. We did note channelling of more severe subjects to ICS medications, as requiring 30 days of treatment and 6 months of treatment attenuated the observed HRs (ICS vs. LABD), though pneumonia was still associated with ICS exposure. In addition, there were higher rates of pneumonia observed among those patents prescribed the highest doses of ICS. Most of the prescribed high-dose ICS was fixed dose combination whereas low-dose was ICS-monotherapy, which could also reflect channelling of more severe subjects to higher dose ICS.

There may be some differences in this observational study relative to clinical trials in terms of the diagnosis of pneumonia. When identifying pneumonia in databases, definitions are based upon existing information collected in routine healthcare which may not include all details measured in clinical trials. In addition, there is lack of agreement between pneumonia classification in the absence of chest x-rays, sputum, etc. Our definitions were based on using HES for hospitalization and built upon prior work (including validation of severe CAP). There may be some confusion between diagnoses of pneumonia versus influenza-related morbidity. However, most pneumonia events in the study were associated with an inpatient hospital admission where pneumonia was recorded as a primary or non-primary cause (95%, 631 of 702 pneumonia events). Therefore, it is likely that pneumonia was more rigorously diagnosed than pneumonia diagnosed in the primary care setting where chest x-rays may not be ordered.

Study Results: : The results of this new-user cohort study design are consistent with published findings that ICS use is associated with increased risk of pneumonia and hospitalized pneumonia in COPD patients treated in the UK. In addition, factors associated with pneumonia included known risk factors such as BMI, age, and co-morbidities.

Unadjusted incidence rates of pneumonia were 48.7 per 1000 person years (PY) among the ICS-containing cohort and 30.9 per 1000 PY among the LABD cohort. Following propensity score adjustment, new use of ICS-containing mediations was associated with an increased risk of pneumonia hospitalization (n=18,047 at risk, n=322 events; HR=1.55 95% CI: 1.14, 2.10) and overall pneumonia (n=18,047 at risk, n=702 events; HR=1.49, 95% CI: 1.22, 1.83). Excess ICS risk was reduced when requiring ≥1 month of new use (all pneumonia: n=17,287 at risk, n=614 events; HR=1.39, 95% CI: 1.12, 1.72) or ≥ 6 months (all pneumonia: ≥6 months; n= 9,396 at risk, n=507 events; HR=1.19, 95% CI: 0.93, 1.52). There was an apparent dose-response with greater risk at higher doses (>1000 mcg/day), however, confidence intervals were overlapping. There was some evidence of channeling bias, with more severe subjects being prescribed ICS, which may not have been fully adjusted in the analysis. Nevertheless, there was an increase in pneumonia associated with ICS.

Demographics/Baseline Characteristics

Variable	**Cohort**				**p-value**
	ICS-Containing Medicines		LABD Medicines		
	n=11,555	%	n=6,492	%	
Male	6,332	54.8	3,778	58.2	<0.01
Age at cohort entry date					
45-64 yrs	3,835	33.2	1,938	29.9	<0.01
65-79 yrs	5,521	47.8	3,316	51.1	.
>=80 yrs	2,199	19.0	1,238	19.1	.
Clinically significant dyspnea diagnosis	948	8.2	1,084	16.7	<0.01
Asthma diagnosis prior to cohort entry date	2,186	18.9	776	12.0	<0.01
Pneumonia episode in year prior to cohort entry	232	2.0	121	1.9	0.50

Primary and Secondary Pneumonia Outcomes from IPTW propensity score model: ICS-containing vs. LABD

Endpoint	ICS-Containing New Users	LABD New Users	Pneumonia Events		IPTW		
	N=	N=	ICS	LABD	HR	LL	UL
Primary Model							
Overall Pneumonia	11,555	6,492	545	157	**1.49**	1.22	1.83
Severe Pneumonia	11,555	6,492	513	147	**1.57**	1.28	1.92
Hospitalized Pneumonia	11,555	6,492	319	90	**1.52**	1.16	1.98
Hospitalized with Pneumonia on the First Episode	11,555	6,492	252	70	**1.55**	1.14	2.10
New use for at least 30 days							
Overall Pneumonia	11,333	5,954	472	142	**1.39**	1.12	1.72
Severe Pneumonia	11,333	5,954	444	133	**1.46**	1.17	1.82
Hospitalized Pneumonia	11,333	5,954	278	84	**1.41**	1.07	1.86
Hospitalized with Pneumonia on the First Episode	11,333	5,954	220	67	**1.40**	1.02	1.92
Persistent user (>6 mo)							
Overall Pneumonia	5,549	3,847	386	121	**1.19**	0.93	1.52
Severe Pneumonia	5,549	3,847	360	115	**1.22**	0.97	1.55
Hospitalized Pneumonia	5,549	3,847	237	74	**1.24**	0.93	1.65
Hospitalized with Pneumonia on the First Episode	5,549	3,847	186	57	**1.23**	0.89	1.72

Logistic Regression: Adjusted Odds Ratios for Any Pneumonia in the Year following Cohort Entry (independent of treatment)

Wald Confidence Interval for Adjusted Odds Ratios			
Effect	**Odds Ratio**	**95% Confidence Limits**	
Age at Cohort Entry	1.043	1.034	1.052
Baseline Pneumonia	2.289	1.646	3.183
CHF in baseline	1.255	1.003	1.570
CVD in Baseline	1.294	1.018	1.644
Peripheral vascular disease	1.295	1.030	1.629
Hemiplagia/Paraplegia diagnosis prior to cohort entry date	2.314	1.007	5.320
Diabetes	1.414	1.112	1.799
Cancer, Non-metastatic	1.436	1.149	1.794
Anxiety diagnosis or Anxiety prescription prior to cohort entry date	1.243	1.046	1.476
SABD in Baseline Period	1.211	1.009	1.452
Statins in Baseline Period	0.767	0.635	0.927
Gender : Male vs Female	1.414	1.201	1.665
Cohort Entry Year 2003 vs 2002	1.099	0.805	1.500
Cohort Entry Year 2004 vs 2002	0.944	0.686	1.299
Cohort Entry Year 2005 vs 2002	1.213	0.887	1.661
Cohort Entry Year 2006 vs 2002	1.313	0.953	1.809
Cohort Entry Year 2007 vs 2002	1.189	0.848	1.667
Cohort Entry Year 2008 vs 2002	1.250	0.903	1.731
Cohort Entry Year 2009 vs 2002	1.435	1.037	1.987
Cohort Entry Year 2010 vs 2002	0.759	0.510	1.130
GOLD Stage 0 vs 2	1.142	0.740	1.760
GOLD Stage 1 vs 2	0.594	0.271	1.304
GOLD Stage 3 vs 2	1.284	0.908	1.816
GOLD Stage 4 vs 2	1.360	0.739	2.504
GOLD Stage Unknown vs 2	1.924	1.484	2.494
BMI <18.5 vs. ≥18.5-21	1.565	1.162	2.107
BMI 21 - <25 vs ≥18.5-21	0.822	0.674	1.002
BMI 25 - <30 vs ≥18.5-25	0.770	0.607	0.977
BMI Unknown vs ≥18.5-25	1.138	0.877	1.477
GERD Diagnosis or Medication in Baseline	1.210	1.024	1.429
Count of emergency hospital admissions in the baseline period 1 vs 0	1.432	1.185	1.731
Count of emergency hospital admissions in the baseline period 2+ vs 0	3.153	2.256	4.406
Count of moderate COPD exacerbations during baseline period 1 vs 0	1.202	1.019	1.418
Count of moderate COPD exacerbations during baseline period 2+ vs 0	2.130	1.541	2.945
Number of severe exacerbations in baseline period 1 vs 0	1.357	1.046	1.759

Conclusions: Among new users, factors associated with pneumonia within the first year independent of treatment included known risk factors such as low BMI, advanced age, severe exacerbation, and co-morbidities. The strongest risk factor for pneumonia was 2 or more emergency hospital admissions in the prior year during baseline (OR=3.2, 95% CI: 2.3-4.4).

- The results of this new-user cohort study design are consistent with published findings that ICS use is associated with increased risk of pneumonia and hospitalized pneumonia in COPD patients treated in the UK.
- New use of ICS-containing mediations was associated with an increased risk of pneumonia relative to LABD (n=18,047 at risk, n=702 events; HR=1.49, 95% CI: 1.22, 1.83)
- Excess ICS risk was attenuated somewhat when requiring ≥30 days of new use (n=17,287 at risk, n=614 events; HR=1.39, 95% CI: 1.12, 1.72) or persistent use (≥6 months; n= 9,396 at risk; n=507 events, HR=1.19, 95% CI: 0.93, 1.52);
- Results were robust and did not vary appreciably when examining more sensitive or more specific pneumonia hospitalization outcomes (e.g., pneumonia hospitalization, pneumonia as primary reason in any episode, pneumonia as a primary reason on the first episode of care)
- There was an apparent dose response, with an increase in risk of pneumonia observed with increasing doses of ICS; however, the confidence intervals between doses overlapped and residual confounding by severity cannot be ruled out as contributing to this trend.
- This risk must be weighed against the benefits when prescribing ICS to patients with COPD.