NOTE: This report contains the summary of findings for the following two studies: WWE113666/WE50001 and WWE111983/WE50002. The two studies are presented together in this single report as they are parallel studies intended to be interpreted together.

| Study No: | WWE113666/WE50001 and WWE111983/WE50002 |
|-----------|-----------------------------------------|

**GSK Medicine:** Fluticasone propionate, beclomethasone dipropionate

| Study No.: | WWE113666/WE50001 |
|------------|--------------------|

| Title: | An Epidemiological Study of Overall Patterns of Use & Outcomes in Users of Fluticasone Propionate (Flonase) Nasal Spray |
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| Rationale: | The study was undertaken as part of a multifaceted epidemiological program to evaluate the utilization, safety and outcomes associated with prescription use of intranasal fluticasone propionate (FP). |
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| Objectives: | The primary objectives were to: 1) characterize intranasal FP and other intranasal steroid (INS) users with respect to demographics and patterns of use; 2) compare the demographic characteristics of fluticasone propionate users with other INS users; 3) to determine the rate of events of interest among patients with intermittent, sub-chronic and chronic FP use episodes compared to patients with intermittent, sub-chronic and chronic episodes of other INS use and 4) assess potential effect modifiers of the association between INS use and events by the use of stratified analysis and to create statistical models including covariates to control for potential confounding variables. |
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| Indication: | Management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older |
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| Study Investigators/Centers: | Research conducted by The Degge Group; principal investigator, Dr. Judith Jones. |
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| Research Methods: | Data Source: The study was conducted in a large US managed care database from i3 Magnifi (formerly Constella Health Strategies), which had claims for approximately six million lives (two million in any given year) in 22 states. Approximately 17 percent of this database's membership belonged to a Medicare Risk plan, which allowed analysis of some of the population over age 65. Roughly four percent of the population belonged to a Medicare Supplement plan; these patients were not included in the analysis due to the possibility of incomplete records. The database contained administrative data, including diagnoses, procedures, prescriptions (NDC, days supply) and hospitalizations. |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------|

| Study Design: | This was an inception cohort study that analysed data from an administrative medical claims database. The two inception cohorts were: 1) patients initiated on intranasal FP and 2) patients initiated on another INS (not FP). The candidates for the inception cohorts did not use any intranasal steroid in the year prior to initiation. The study period was January 1, 1995 through September 30, 2002. Patient records dated between January 1, 1994 and September 30, 2002 were used to develop the overall study cohort. |
|------------------|----------------------------------------------------------------------------------------------------------------------------------|

| Study Population: | Overall cohort eligibility was based on meeting criteria for continuous coverage in the medical claims database, such that it was reasonable to assume that patients' medical care was received from the health plan and that the occurrence of events was reliably captured in the database. Eligibility interruptions of 30 days or less were assumed to be simple administrative lags in data entry. In these cases, eligibility intervals on either side of the interruption were combined into one continuous interval. All patients were required to have at least 12 months of continuous eligibility before the index date. When patient history was divided into FP or other INS use episodes, there had to be at least 120 days of plan eligibility after the last prescription claim in the episode to be included in the outcome analysis. The index date was the first FP prescription claim or the first INS prescription claim (other than FP). The first prescription claim determined cohort placement. Additionally, the first episode (containing the index date) must have at least 120 days after the last prescription claim free from exposure to another intranasal steroid. If a patient received another intranasal steroid after the index date, he or she was censored at that point in time. (Of note, patients within the other INS cohort were allowed to switch between (non-fluticasone propionate) INS therapies without being censored) |
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Patients under four years of age at index date were excluded from the cohort.

Medical claims and patient eligibility data were linked with a unique encrypted patient identification number by the data vendor. The Degge Group had access to only the encrypted patient identification number and therefore, patient confidentiality was maintained at all times.

| Study Exposures, Outcomes: | This study evaluated outcomes in patients exposed to FP and other INS. A continuous interval of exposure to FP or other INS was defined as a the time period covered by a series of prescription claims having no more than 60 days between any two consecutive claims. FP and other INS exposure episodes were identified within all eligible patient histories as 1) intermittent exposure episode defined as a continuous interval of |
exposure to the same drug consisting of 1, 2, or 3 continuous prescription claims; 2) sub-chronic use episode defined as a continuous interval of exposure to the same drug consisting of 4, 5, 6, 7, or 8 continuous prescription claims or 3) chronic use episode defined as a continuous interval of exposure to the same drug consisting of 9 or more continuous prescription claims. A span of at least six months had to occur between the first and last prescription claim.

The following outcomes were investigated:

| Outcome                                                                 |
|-------------------------------------------------------------------------|
| Cataracts                                                               |
| Glaucoma                                                                |
| Nasal septum perforation                                                |
| Hypercorticism (Cushing's)                                              |
| Adrenal insufficiency                                                   |
| Fractures (limited to hip, wrist and vertebral) as proxies for osteoporosis |
| Osteoporosis                                                            |
| Sinusitis (acute and chronic)                                           |
| Infectious complications of sinusitis to include:                       |
| Cellulitis (periorbital)                                                |
| Empyema (maxillary)                                                     |
| Abscess (brain)                                                         |
| Meningitis                                                              |
| Encephalitis                                                            |

**Data Analysis Methods:** For the descriptive analyses, patients in the FP and other INS cohorts were compared on the basis of sex, age group (10 year age ranges), geographic region of residence, seasonality (by month) of use of first INS prescription, various risk factors for each outcome, the number of inhaled and oral corticosteroid prescriptions in the year prior to the index date, the number of INS prescriptions per year and average number of days between prescription refills (stratified by eligible time).

To analyze events, episodes were created within each patient’s claims history. Episodes of FP or other INS exposure are defined as any series of prescriptions filled within 60 days of one another. A break of more than 60 days constituted a separate episode. Observation periods to capture incident events began with the first prescription filled in the episode and terminated 120 days (30 days to complete dose plus a 90 day observance tail) after the last fill date. Episodes with exposures to another study medication during the 120 day assessment period were excluded. Of note, episodes containing a subsequent exposure(s) to the same INS after 60 days from the last fill date were not censored. Only one episode per person was be evaluated; that episode was randomly selected from the eligible episodes. Person-time exposure accumulated from the episode index date to an event claim date or 120 days after the last fill date within that prescription series, which ever occurred first.

Additionally, a sensitivity analysis was conducted excluding patients with any corticosteroid use in the prior year.

Rates and rate ratios with 95% confidence intervals were calculated for events in the intermittent, sub-chronic and chronic FP and other INS episode groups. If an event was present, the investigator assessed exposure status in the months prior to the event, counting the number of prescriptions and amount of time that preceded the event. Depending on the number of prescriptions observed and duration of use, events were grouped into an exposure episode. Each event (or event group) was analyzed separately. Patients with an event of interest during the 12 months prior to their entry into the cohort or during the 12 months prior to an episode index date were automatically excluded from the analysis of that event. This exclusion criterion was applied to rule out prevalent conditions. For glaucoma, drug codes were used as a proxy measure for diagnosis codes that were recorded in the patient’s medical history.

In order to assess potential effect modifiers of the association between INS use and events, the following variables were stratified: 1) the duration of use (intermittent, sub-chronic, chronic); 2) concurrent oral and/or inhaled corticosteroid use (intranasal only, intranasal and current inhaled, intranasal and current oral, intranasal and current inhaled + oral); 3) past steroid use (inhaled and/or oral, recent and/or remote past); 4) drug interactions (INS and concurrent ritonavir, ketoconazole or itraconazole use).

Additionally, covariates were added to the statistical model in order to control for potential confounders. The covariates used in each model were endpoint specific, such that they would be both associated with the endpoint and
with the probability of receiving an intranasal FP prescription. To be included in the analysis, comorbid conditions must have been diagnosed prior to the episode index date.

A historical cohort study design was used to analyze the association between the selected outcomes and INS use. Poisson regression modeling was used to estimate the relative rate adjusting for the potential confounders and to calculate the associated 95% confidence intervals (CIs). A manual stepwise regression procedure was used to identify those risk factors / modifiers that were independently associated with the endpoint event under evaluation. A threshold of P < 0.1 will be used for inclusion into the model. Covariates known to be major contributing factors were forced in the model, regardless of the results of their statistical significance. An alpha level of 0.05 was used to test for statistical significance. Analyses were performed using SAS (Version 8.02; SAS Institute, Cary, NC, USA).

**Limitations:** Medicare data claims are generally not captured in insurance claims databases, and therefore, patients 65 years of age and older were under-represented. Studies in i3 Magnifi (formerly Constella Health Strategies) database was mostly focused on patients 65 and under. i3 Magnifi's data prior to 2001 included some Medicare Risk plans and patients over 65 which were included (though underrepresented) in the sample.

Another limitation of this database studies is that laboratory data—used for disease diagnosis—were not available for study. Currently such databases are in developmental stages and do not cover a large number of patients.

**Study Results:** There were a total of 126,613 patients eligible to participate in the study. Of this total, 52,870 patients were in the FP cohort and 73,743 patients were in the INS cohort (cohorts mutually exclusive). The mean age of the FP cohort was 43 (SD ± 20) years of age and the mean age of the INS cohort was 45 (SD ± 21) years of age. Females comprised 59% of both cohorts and men comprised 41%. Regarding the regional distribution of patients, the largest concentration of patients were from the South (~ 67%), followed by the Midwest (~ 30%), West (~ 3%), and Northeast regions (~ 0.2). Concerning seasonal trends, a similar proportion of patients received their first FP/INS prescription throughout the seasons (winter, spring, summer, fall), ranging from 20% – 29% each season.

Nearly 86% of patients in the FP cohort and 84% of patients in the INS cohort received only one prescription during the selected episode/study. Of the 126,613 patients, roughly 97% of FP and INS patients were categorized as intermittent users, 2.5% as sub-chronic users, and 0.5% as chronic users. Factoring in the exposure time and 90 day observation period, the 52,870 FP patients accounted for 18,884 person-years and the 73,743 patients in the INS cohort accounted for 26,429 person-years of observation.

Thirteen outcomes associated with corticosteroid use were evaluated in FP patients as compared to INS patients. These outcomes included: adrenal insufficiency, cataracts, fracture, glaucoma, hypercorticism, nasal septum perforation, osteoporosis, sinusitis, abscess, cellulitis, empyema, encephalitis, and meningitis. For the various outcomes, several variables were assessed and incorporated into the multivariate statistical model to control for potential confounding. After adjusting for these factors, five outcomes were more likely to occur in FP patients than INS patients. These included hypercorticism, nasal septum perforation, sinusitis, abscess, and empyema. FP patients were 2.6 times (95% confidence interval (CI), 1.21-5.59; p ≤ 0.01) more likely to have received a diagnosis for hypercorticism than INS patients. Nasal septum perforation was 1.10 times (95% CI, 1.00-1.22; p < 0.05) more likely to occur in FP than INS patients. Sinusitis was 1.10 times (95% CI, 1.07-1.14; p ≤ 0.01) more likely to occur in FP than INS patients. Abscess was 1.13 times (95% CI, 1.07-1.20; p ≤ 0.01) more likely to occur in FP than INS patients. Finally, empyema was 2.20 times (95% CI, 1.27-3.83; p ≤ 0.01) more likely to occur in FP than INS patients. In contrast, FP patients were less likely to have received a diagnosis for cataracts than patients taking other INS (adjusted rate ratio (aRR), 0.80; 95% CI, 0.71-0.89; p ≤ 0.01). All other outcomes assessed were not found to be statistically different between the FP and INS cohorts.

Several stratification analyses were conducted to further assess the effect of various factors on the outcome. These factors included: episode type (intermittent, sub-chronic, and chronic use), concurrent oral corticosteroid use, and interacting drugs.

As stated previously, roughly 97% of FP and INS patients were categorized as intermittent users, 2.5% as sub-chronic users, and 0.5% as chronic users. After stratification, intermittent users were found to have roughly the same adjusted and unadjusted rate ratios as the overall analyses. All outcomes that were statistically significant in the overall analyses were significant in the intermittent user subgroup, with the exception of nasal septum perforation (aRR, 1.10; 95% CI, 1.00-1.21; p = 0.06). All sub-chronic and chronic exposure subcategories were not found to be statistically different for any of the outcomes, with the exception cataracts (sub-chronic: aRR 0.55; 95% CI, 0.32-0.94; p < 0.05). Several of the adjusted and unadjusted results for sub-chronic and chronic users were not able to be calculated due to
the limited number of patients and outcomes in these categories.

Roughly, 85% of FP and INS patients did not have an inhaled corticosteroid (ICS) or oral corticosteroid (OCS) dispensing during a FP or INS episode. Approximately 8% of FP and INS patients were dispensed concomitant OCS, 4% had concomitant ICS, and 2% had concomitant ICS/OCS dispensings during the episode. For the subgroup of INS patients without a concomitant steroid, the adjusted rate ratios slightly increased for three of the outcomes found to be statistically significant in the overall analyses: nasal septum perforation, sinusitis, and abscess. Similarly, when comparing FP to INS patients, the adjusted ratio for cataracts was found to have decreased slightly (aRR, 0.76; 95% CI, 0.67-0.85; p = 0.01). In contrast, when excluding patients taking concomitant steroids, the adjusted rate ratios for hypercorticism and empyema decreased and were not statistically significant (aRR, 2.12; 95% CI, 0.75-5.97; p = 0.16 and aRR, 1.60; 95% CI, 0.87-2.94; p = 0.18, respectively). All other outcomes by corresponding sub-groupings (INS only, ICS, OCS, and ICS/OCS) were different between FP and INS users.

To further explore the effect of episode type and concurrent corticosteroid (ICS or OCS) use, patients were divided in categories by episode type and steroid use. Due to the limited number of patients and events in sub-chronic, chronic, and concurrent steroid subcategories, the results from the adjusted analyses and several of the unadjusted analyses are not available. Thus, the adjusted rate ratios are provided for only intermittent non-concomitant corticosteroid users. The unadjusted rate ratios are provided for all subgroups with at least one event in the FP and INS cohorts. With regards to intermittent non-concomitant steroid users, virtually the same rate-ratios as non-concomitant steroid users were found. FP users in the intermittent non-concomitant steroid subgroup were more likely to have nasal perforation, sinusitis, and abscess than INS users. Additionally, FP users in the intermittent non-concomitant steroid subgroup were less likely to have cataracts than INS users. Empyema and hypercorticism, two outcomes in the overall analysis found to be statistically more likely to occur in the FP group as compared to the INS group, were no longer significant in this subgroup. All other rate ratios for each of the outcomes were not found to be statistically different between FP and INS users.

Less than 1% of FP and INS patients took concomitant itraconazole, ketoconazole, and/or ritonavir (interacting drugs) during the study. Thus, due to the small number of patients taking these medications and the small number of associated events, many of the unadjusted and all of the adjusted rate ratios are not available for these patients. When patients taking interacting drugs were removed from the outcome analyses (INS only), virtually the same rate-ratios as those found in the analyses including these patients. Additionally, due to the limited numbers in the subgroups the analyses stratified by episode type and interacting drugs did not provide any pertinent results. The unadjusted and adjusted rate ratios for intermittent, sub-chronic, and chronic patients not taking an interacting drug (INS only) yielded virtually identical results as all intermittent, sub-chronic, and chronic patients.

| Table 1. Distribution of patients by demographic characteristics and Cohort Grouping |
|-----------------------------------------------|--------|--------|--------|--------|--------|--------|
| Characteristics | FP Cohort # Patients | % Patients | INS Cohort # Patients | % Patients | All Patients # Patients | % Patients |
| All Patients | 52,870 | 100.0 | 73,743 | 100.0 | 126,613 | 100.0 |
| Female | 30,993 | 58.6 | 43,498 | 59.0 | 74,491 | 58.8 |
| 4-14 | 2,701 | 5.1 | 4,020 | 5.5 | 6,721 | 5.3 |
| 15-24 | 2,427 | 4.6 | 3,147 | 4.3 | 5,574 | 4.4 |
| 25-34 | 4,300 | 8.1 | 5,017 | 6.8 | 9,317 | 7.4 |
| 35-44 | 6,527 | 12.3 | 8,730 | 11.8 | 15,257 | 12.1 |
| 45-54 | 6,561 | 12.4 | 8,805 | 11.9 | 15,366 | 12.1 |
| 55-64 | 3,680 | 7.0 | 4,857 | 6.6 | 8,537 | 6.7 |
| 65-74 | 2,865 | 5.4 | 5,003 | 6.8 | 7,868 | 6.2 |
| 75-84 | 1,522 | 2.9 | 3,092 | 4.2 | 4,614 | 3.6 |
| 85+ | 410 | 0.8 | 827 | 1.1 | 1,237 | 1.0 |
| Male | 21,877 | 41.4 | 30,245 | 41.0 | 52,122 | 41.2 |
| 4-14 | 3,054 | 5.8 | 4,731 | 6.4 | 7,785 | 6.1 |
| 15-24 | 1,842 | 3.5 | 2,185 | 3.0 | 4,027 | 3.2 |
| 25-34 | 2,542 | 4.8 | 3,101 | 4.2 | 5,643 | 4.5 |
| 35-44 | 4,300 | 8.1 | 5,336 | 7.2 | 9,636 | 7.6 |
| Eligibility time person-months | Number of randomly selected episodes | Patient-years accrued during the episodes | Number of randomly selected episodes | Patient-years accrued during the window |
|-------------------------------|--------------------------------------|------------------------------------------|-------------------------------------|----------------------------------------|
| 4 to < 6                      | 50,401                               | 17,041                                   | 70,309                              | 23,807                                 |
| 6 to < 12                     | 2,134                                | 1,367                                    | 2,913                               | 1,863                                  |
| 12 to < 24                    | 298                                  | 375                                      | 455                                 | 587                                    |
| 24 to < 36                    | 22                                   | 50                                       | 53                                  | 121                                    |
| 36 to < 48                    | 13                                   | 43                                       | 8                                   | 27                                     |
| 48 to < 60                    | 2                                    | 9                                        | 2                                   | 9                                      |
| >= 60                         | 0                                    | 0                                        | 3                                   | 16                                     |
| Totals                        | 52,870                               | 18,884                                   | 73,743                              | 26,429                                 |

* Eligibility time refers to the time observed within the randomly selected episode, regardless of outcomes prior to end of episode.

| Eligibility time person-months | Avg. number of prescriptions per Year | Avg. number of days between refills** | Avg. number of prescriptions per Year | Avg. number of days between refills** |
|-------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|----------------------------------------|
| 4 to < 6                      | 3                                    | 34                                   | 3                                  | 30                                     |
| 6 to < 12                     | 6                                    | 38                                   | 6                                  | 37                                     |
| 12 to < 24                    | 8                                    | 37                                   | 9                                  | 35                                     |
| 24 to < 36                    | 9                                    | 37                                   | 10                                 | 34                                     |
| 36 to < 48                    | 10                                   | 35                                   | 11                                 | 30                                     |
| 48 to < 60                    | 11                                   | 32                                   | 12                                 | 29                                     |
| >= 60                         | 0                                    | 0                                    | 13                                 | 27                                     |
| Totals                        | 3                                    | 35                                   | 3                                  | 32                                     |
** Only 7,503 FP patients are included in the calculation of average time in between refills. 45,377 patients only had 1 prescription.

*** Only 11,643 INS patients are included in the calculation of average time in between refills. 62,100 patients only had 1 prescription.

Table 2c. Number of FP/INS prescriptions during the randomly selected episodes.

| Number of Prescriptions | FP Cohort | INS Cohort |
|-------------------------|-----------|------------|
| # Patients              | % Patients | # Patients | % Patients |
| 1                       | 45,369    | 85.8       | 62,100     | 84.2       |
| 2                       | 4,660     | 8.8        | 7,333      | 9.9        |
| 3                       | 1,311     | 2.5        | 2,009      | 2.7        |
| 4                       | 568       | 1.1        | 832        | 1.1        |
| 5                       | 312       | 0.6        | 437        | 0.6        |
| 6+                      | 650       | 1.2        | 1,032      | 1.4        |
| Totals                  | 52,870    | 100.0      | 73,743     | 100.0      |

Table 3. Event Rates and Rate Ratios (Random Episodes)

| Events                  | FP Cohort (n= 52,870)* | INS Cohort (n=73,743) | Rate Ratios |
|-------------------------|------------------------|------------------------|-------------|
|                         | # of Events | PY | Rate / 10,000 PY | # of Events | PY | Rate / 10,000 PY | Rate Ratio (95% CI) | Adjusted Rate Ratio (95% CI) |
| Adrenal Insufficiency   | 14          | 18,701 | 7 | 13 | 26,224 | 5 | 1.51 (0.71 - 3.21) | 1.57 (0.74 - 3.35) |
| Cataract                | 483         | 18,088 | 267 | 992 | 24,785 | 400 | 0.67 (0.60 - 0.74) | 0.80 (0.71 - 0.89) |
| Fracture                | 134         | 18,714 | 72 | 180 | 26,184 | 69 | 1.04 (0.83 - 1.30) | 1.10 (0.88 - 1.38) |
| Glaucoma                | 241         | 18,294 | 132 | 378 | 25,400 | 149 | 0.89 (0.75 - 1.04) | 0.97 (0.83 - 1.15) |
| Hypercorticism          | 19          | 18,845 | 10 | 10 | 26,387 | 4 | 2.66 (1.24 - 5.72) | 2.59 (1.21 - 5.59) |
| Nasal Septum Perforation| 745         | 17,998 | 414 | 939 | 25,382 | 370 | 1.12 (1.02 - 1.23) | 1.10 (1.00 - 1.22) |
| Osteoporosis            | 59          | 18,775 | 31 | 79 | 26,315 | 30 | 1.05 (0.75 - 1.47) | 1.08 (0.77 - 1.52) |
| Sinusitis               | 5,870       | 12,719 | 4,615 | 7,710 | 18,556 | 4,155 | 1.11 (1.07 - 1.15) | 1.10 (1.07 - 1.14) |
| Abscess                 | 2,076       | 15,503 | 1,339 | 2,562 | 21,977 | 1,166 | 1.15 (1.08 - 1.21) | 1.13 (1.07 - 1.20) |
| Cellulitis              | 36          | 18,837 | 19 | 60 | 26,371 | 23 | 0.84 (0.56 - 1.27) | 0.84 (0.56 - 1.27) |
| Empyema                 | 30          | 18,859 | 16 | 22 | 26,401 | 8 | 1.91 (1.10 - 3.31) | 2.20 (1.27 - 3.83) |
| Encephalitis            | 5           | 18,879 | 3 | 3 | 26,426 | 1 | 2.33 (0.56 - 9.76) | 2.19 (0.52 - 9.26) |
| Meningitis              | 8           | 18,869 | 4 | 18 | 26,412 | 7 | 0.62 (0.27 - 1.43) | 0.63 (0.27 - 1.45) |

† p ≤ 0.01 (INS control)
‡ p < 0.05 (INS control)

Table 4. Event Rates and Rate Ratios by Event and Episode Type (Random Episode)
| Event                        | Episode Type       | Rate / 10,000 PY | Rate / 10,000 PY | Rate Ratio (95% CI) | Adjusted Rate Ratio (95% CI) |
|------------------------------|--------------------|------------------|------------------|---------------------|------------------------------|
| Adrenal Insufficiency        | intermittent       | 8                | 5                | 1.63(0.75-3.52)     | 1.68(0.77-3.64)               |
|                             | sub-chronic        | 0                | 8                | N/A                 | N/A                          |
|                             | chronic            | 0                | 0                | N/A                 | N/A                          |
| Cataract                     | intermittent       | 272              | 401              | 0.68(0.61-0.76)†    | 0.81(0.72-0.91)†              |
|                             | sub-chronic        | 225              | 439              | 0.51(0.30-0.87)‡    | 0.55(0.32-0.94)‡              |
|                             | chronic            | 132              | 293              | 0.45(0.17-1.22)     | N/A                          |
| Fracture                     | intermittent       | 73               | 67               | 1.08(0.86-1.37)     | 1.14(0.90-1.44)               |
|                             | sub-chronic        | 55               | 78               | 0.71(0.24-2.07)     | N/A                          |
|                             | chronic            | 51               | 104              | 0.49(0.10-2.34)     | N/A                          |
| Glaucoma                     | intermittent       | 133              | 150              | 0.89(0.75-1.05)     | 0.98(0.83-1.15)               |
|                             | sub-chronic        | 127              | 147              | 0.86(0.41-1.83)     | N/A                          |
|                             | chronic            | 77               | 94               | 0.82(0.20-3.28)     | N/A                          |
| Hypercorticism               | intermittent       | 10               | 4                | 2.51(1.16-5.43)‡    | 2.43(1.12-5.27)‡              |
|                             | sub-chronic        | 11               | 0                | N/A                 | N/A                          |
|                             | chronic            | 0                | 0                | N/A                 | N/A                          |
| Nasal Septum Perforation     | intermittent       | 431              | 388              | 1.11(1.01-1.22)‡    | 1.10(1.00-1.21)               |
|                             | sub-chronic        | 200              | 189              | 1.06(0.57-1.98)     | N/A                          |
|                             | chronic            | 132              | 46               | 2.86(0.68-12.0)     | N/A                          |
| Osteoporosis                 | intermittent       | 33               | 30               | 1.12(0.79-1.59)     | 1.16(0.82-1.64)               |
|                             | sub-chronic        | 11               | 39               | 0.29(0.03-2.44)     | N/A                          |
|                             | chronic            | 0                | 29               | N/A                 | N/A                          |
| Sinusitis                    | intermittent       | 4,855            | 4,399            | 1.10(1.07-1.14)†    | 1.10(1.06-1.14)†              |
|                             | sub-chronic        | 1,198            | 1,264            | 0.95(0.70-1.28)     | N/A                          |
|                             | chronic            | 777              | 542              | 1.43(0.78-2.63)     | N/A                          |
| Abscess                      | intermittent       | 1,311            | 1,147            | 1.14(1.08-1.21)†    | 1.13(1.07-1.20)†              |
|                             | sub-chronic        | 500              | 564              | 0.89(0.60-1.31)     | N/A                          |
|                             | chronic            | 407              | 200              | 2.03(0.94-4.40)     | N/A                          |
| Cellulitis                   | intermittent       | 21               | 24               | 0.85(0.56-1.29)     | 0.85(0.56-1.29)               |
| Event                  | Concurrent Steroid Use | FP Cohort (n=52,870) Rate / 10,000 PY | INS Cohort (n=73,743) Rate / 10,000 PY | Rate Ratios | Adjusted Rate Ratio |
|------------------------|------------------------|---------------------------------------|----------------------------------------|-------------|---------------------|
|                        |                        | Rate Ratio (95% CI)                   | Adjusted Rate Ratio (95% CI)           |             |                     |
| Adrenal Insufficiency  | INS only               | 7                                     | 4                                     | 1.54(0.66-3.63) | 1.61(0.68-3.79)     |
|                        | ICS                    | 13                                    | 17                                    | 0.77(0.07-8.48) | N/A                 |
|                        | OCS                    | 12                                    | 5                                     | 2.64(0.24-29.1) | N/A                 |
|                        | ICS & OCS              | 0                                     | 0                                     | N/A          | N/A                 |
| Cataract               | INS only               | 262                                   | 418                                   | 0.63(0.56-0.70)‡ | 0.76(0.67-0.85)‡    |
|                        | ICS                    | 346                                   | 355                                   | 0.97(0.59-1.61) | N/A                 |
|                        | OCS                    | 294                                   | 252                                   | 1.17(0.79-1.73) | N/A                 |
|                        | ICS & OCS              | 212                                   | 358                                   | 0.59(0.26-1.36) | N/A                 |
| Fracture               | INS only               | 66                                    | 67                                    | 0.98(0.76-1.26) | 1.04(0.81-1.34)     |
|                        | ICS                    | 106                                   | 52                                    | 2.05(0.71-5.91) | N/A                 |
|                        | OCS                    | 108                                   | 82                                    | 1.31(0.68-2.52) | N/A                 |
|                        | ICS & OCS              | 75                                    | 102                                   | 0.74(0.18-2.95) | N/A                 |
| Glaucoma               | INS only               | 133                                   | 153                                   | 0.87(0.73-1.04) | 0.97(0.81-1.15)     |
|                        | ICS                    | 108                                   | 143                                   | 0.76(0.32-1.77) | N/A                 |
|                        | OCS                    | 123                                   | 99                                    | 1.24(0.67-2.29) | N/A                 |
|                        | ICS & OCS              | 154                                   | 196                                   | 0.79(0.29-2.13) | N/A                 |
| Hypercorticism         | INS only               | 6                                     | 3                                     | 2.10(0.75-5.91) | 2.12(0.75-5.97)     |
|                        | ICS                    | 13                                    | 0                                     | N/A          | N/A                 |

N/A: Rate Ratios with insufficient number of events to provide meaningful results.

† p ≤ 0.01 (INS control)
‡ p < 0.05 (INS control)

Table 5. Event Rates and Rate Ratios by Event and Concurrent Steroid Use (Random Episode)
| Event Type               | FP Cohort (n=52,870) | INS Cohort (n=73,743) | Rate Ratios                        |
|-------------------------|----------------------|-----------------------|------------------------------------|
| Nasal Septum Perforation|                      |                       |                                    |
| INS only                | 409 347              | 1.18(1.06-1.31)†      | 1.17(1.05-1.30)†                   |
| ICS                     | 192 223              | 0.86(0.45-1.66)       | N/A                                |
| OCS                     | 597 724              | 0.82(0.64-1.07)       | N/A                                |
| ICS & OCS               | 294 254              | 1.16(0.53-2.55)       | N/A                                |
| Osteoporosis            |                      |                       |                                    |
| INS only                | 30 28                | 1.09(0.74-1.58)       | 1.13(0.77-1.65)                    |
| ICS                     | 66 43                | 1.54(0.45-5.33)       | N/A                                |
| OCS                     | 24 50                | 0.48(0.15-1.50)       | N/A                                |
| ICS & OCS               | 50 17                | 2.93(0.27-32.3)       | N/A                                |
| Sinusitis               |                      |                       |                                    |
| INS only                | 4,913 4,384          | 1.12(1.08-1.16)†      | 1.11(1.07-1.15)†                   |
| ICS                     | 1,820 2,049          | 0.89(0.69-1.14)       | N/A                                |
| OCS                     | 3,596 3,435          | 1.05(0.91-1.20)       | N/A                                |
| ICS & OCS               | 1,801 1,753          | 1.03(0.71-1.50)       | N/A                                |
| Abscess                 |                      |                       |                                    |
| INS only                | 1,283 1,098          | 1.17(1.10-1.24)†      | 1.15(1.08-1.23)†                   |
| ICS                     | 878 716              | 1.23(0.87-1.72)       | N/A                                |
| OCS                     | 1,296 1,348          | 0.96(0.79-1.16)       | N/A                                |
| ICS & OCS               | 628 772              | 0.81(0.48-1.37)       | N/A                                |
| Cellulitis              |                      |                       |                                    |
| INS only                | 19 21                | 0.92(0.59-1.45)       | 0.93(0.59-1.46)                    |
| ICS                     | 26 34                | 0.77(0.14-4.19)       | N/A                                |
| OCS                     | 18 32                | 0.56(0.15-2.18)       | N/A                                |
| ICS & OCS               | 0 34                 | N/A                   | N/A                                |
| Empyema                 |                      |                       |                                    |
| INS only                | 13 9                 | 1.40(0.76-2.56)       | 1.60(0.87-2.94)                    |
| ICS                     | 65 0                 | N/A                   | N/A                                |
| OCS                     | 24 5                 | 5.26(0.59-47.0)       | N/A                                |
| ICS & OCS               | 0 0                  | N/A                   | N/A                                |
| Encephalitis            |                      |                       |                                    |
| INS only                | 3 1                  | 2.33(0.56-9.77)       | 2.28(0.54-9.63)                    |
| ICS                     | 0 0                  | N/A                   | N/A                                |
| OCS                     | 0 0                  | N/A                   | N/A                                |
| ICS & OCS               | 0 0                  | N/A                   | N/A                                |
| Meningitis              |                      |                       |                                    |
| INS only                | 4 7                  | 0.53(0.21-1.34)       | 0.53(0.20-1.36)                    |
| ICS                     | 0 0                  | N/A                   | N/A                                |
| OCS                     | 12 5                 | 2.63(0.24-29.0)       | N/A                                |
| ICS & OCS               | 0 0                  | N/A                   | N/A                                |

N/A: Rate Ratios with insufficient number of events to provide meaningful results.

† p ≤ 0.01 (INS control)
‡ p < 0.05 (INS control)

Table 6. Event Rates and Rate Ratios by Episode Type and Concurrent Steroid Use (Random Episode)
| Event Type | Episode Type | Current Steroid Use | Rate / 10,000 PY | Rate / 10,000 PY | Rate Ratio (95% CI) | Adjusted Rate Ratio (95% CI)* |
|------------|--------------|---------------------|------------------|------------------|---------------------|-----------------------------|
|            |              | INS only            | 7                | 5                | 1.54(0.65-3.62)     | 1.60(0.68-3.79)             |
|            |              | ICS                 | 15               | 10               | 1.50(0.09-23.9)     | N/A                         |
| Adrenal Insufficiency |            | OCS                 | 14               | 5                | 2.61(0.24-28.7)     | N/A                         |
|            |              | ICS & OCS           | 0                | 0                | N/A                 | N/A                         |
|            | sub-chronic | INS only            | 0                | 0                | N/A                 | N/A                         |
|            |              | ICS                 | 0                | 85               | N/A                 | N/A                         |
|            |              | OCS                 | 0                | 0                | N/A                 | N/A                         |
|            |              | ICS & OCS           | 0                | 0                | N/A                 | N/A                         |
|            | chronic     | INS only            | 0                | 0                | N/A                 | N/A                         |
|            |              | ICS                 | 0                | 0                | N/A                 | N/A                         |
|            |              | OCS                 | 0                | 0                | N/A                 | N/A                         |
|            |              | ICS & OCS           | 0                | 0                | N/A                 | N/A                         |
| Cataract   | intermittent| INS only            | 267              | 417              | 0.64(0.57-0.72)*    | 0.77(0.68-0.87)*            |
|            |              | ICS                 | 364              | 386              | 0.94(0.56-1.59)     | N/A                         |
|            |              | OCS                 | 300              | 258              | 1.16(0.77-1.76)     | N/A                         |
|            |              | ICS & OCS           | 210              | 271              | 0.77(0.29-2.09)     | N/A                         |
|            | sub-chronic | INS only            | 212              | 477              | 0.44(0.24-0.83)     | N/A                         |
|            |              | ICS                 | 0                | 180              | N/A                 | N/A                         |
|            |              | OCS                 | 369              | 203              | 1.82(0.41-8.14)     | N/A                         |
|            |              | ICS & OCS           | 372              | 908              | 0.41(0.08-2.03)     | N/A                         |
|            | chronic     | INS only            | 115              | 320              | 0.36(0.10-1.27)     | N/A                         |
|            |              | ICS                 | 857              | 182              | 4.72(0.43-52.0)     | N/A                         |
|            |              | OCS                 | 0                | 221              | N/A                 | N/A                         |
|            |              | ICS & OCS           | 0                | 340              | N/A                 | N/A                         |
| Fracture   | intermittent| INS only            | 67               | 65               | 1.03(0.79-1.33)     | 1.09(0.84-1.41)             |
|            |              | ICS                 | 91               | 51               | 1.79(0.55-5.88)     | N/A                         |
|            |              | OCS                 | 121              | 83               | 1.46(0.75-2.87)     | N/A                         |
|            |              | ICS & OCS           | 100              | 135              | 0.74(0.19-2.96)     | N/A                         |
|            | sub-chronic | INS only            | 62               | 76               | 0.81(0.24-2.78)     | N/A                         |
|            |              | ICS                 | 134              | 83               | 1.61(0.10-25.7)     | N/A                         |
|            |              | OCS                 | 0                | 125              | N/A                 | N/A                         |
| Condition          | Type     | ICS & OCS | INS only | ICS | OCS | ICS & OCS | GEE 95% CI  | OCS & GEE 95% CI  |
|--------------------|----------|-----------|----------|-----|-----|-----------|-------------|-------------------|
| Glaucoma           | intermittent | 0 | 0       | N/A | N/A |
|                    |           |           | INS only | 37  | 159 | 0.23(0.03-1.90) | N/A         |
|                    |           |           | ICS     | 390 | 0   | N/A       | N/A         |
|                    |           |           | OCS     | 0   | 0   | N/A       | N/A         |
|                    |           |           | ICS & OCS | 0  | 0   | N/A       | N/A         |
| Glaucoma           | sub-chronic | 0 | 0       | N/A | N/A |
|                    |           |           | INS only | 136 | 154 | 0.88(0.74-1.05) | 0.98(0.82-1.17) |
|                    |           |           | ICS     | 109 | 137 | 0.80(0.32-2.00) | N/A         |
|                    |           |           | OCS     | 110 | 102 | 1.08(0.56-2.10) | N/A         |
|                    |           |           | ICS & OCS | 171 | 212 | 0.81(0.27-2.41) | N/A         |
| Glaucoma           | chronic   | 0 | 0       | N/A | N/A |
|                    |           |           | INS only | 76  | 96  | 0.79(0.15-4.33) | N/A         |
|                    |           |           | ICS     | 0   | 0   | N/A       | N/A         |
|                    |           |           | OCS     | 165 | 104 | 1.58(0.10-25.3) | N/A         |
|                    |           |           | ICS & OCS | 0  | 151 | N/A       | N/A         |
| Glaucoma           | intermittent | 0 | 0       | N/A | N/A |
|                    |           |           | INS only | 96  | 147 | 0.65(0.25-1.71) | N/A         |
|                    |           |           | ICS     | 144 | 265 | 0.54(0.06-5.22) | N/A         |
|                    |           |           | OCS     | 265 | 64  | 4.18(0.43-40.2) | N/A         |
|                    |           |           | ICS & OCS | 170 | 141 | 1.20(0.08-19.2) | N/A         |
| Glaucoma           | sub-chronic | 0 | 0       | N/A | N/A |
|                    |           |           | INS only | 0   | 0   | N/A       | N/A         |
|                    |           |           | ICS     | 0   | 0   | N/A       | N/A         |
|                    |           |           | OCS     | 0   | 0   | N/A       | N/A         |
|                    |           |           | ICS & OCS | 0  | 151 | N/A       | N/A         |
| Glaucoma           | chronic   | 0 | 0       | N/A | N/A |
|                    |           |           | INS only | 6   | 3   | 2.09(0.75-5.88) | 2.12(0.75-5.98) |
|                    |           |           | ICS     | 15  | 0   | N/A       | N/A         |
|                    |           |           | OCS     | 47  | 10  | 4.55(0.94-21.9) | N/A         |
|                    |           |           | ICS & OCS | 33  | 45  | 0.74(0.07-8.11) | N/A         |
| Glaucoma           | intermittent | 0 | 0       | N/A | N/A |
|                    |           |           | INS only | 0   | 0   | N/A       | N/A         |
|                    |           |           | ICS     | 0   | 0   | N/A       | N/A         |
|                    |           |           | OCS     | 0   | 0   | N/A       | N/A         |
|                    |           |           | ICS & OCS | 0  | 0   | N/A       | N/A         |
| Glaucoma           | sub-chronic | 0 | 0       | N/A | N/A |
|                    |           |           | INS only | 0   | 0   | N/A       | N/A         |
|                    |           |           | ICS     | 0   | 0   | N/A       | N/A         |
|                    |           |           | OCS     | 0   | 0   | N/A       | N/A         |
|                    |           |           | ICS & OCS | 0  | 0   | N/A       | N/A         |
| Glaucoma           | chronic   | 0 | 0       | N/A | N/A |
|                    |           |           | INS only | 0   | 0   | N/A       | N/A         |
|                    |           |           | ICS     | 0   | 0   | N/A       | N/A         |
|                    |           |           | OCS     | 0   | 0   | N/A       | N/A         |
|                    |           |           | ICS & OCS | 0  | 0   | N/A       | N/A         |
| Nasal Perforation  | intermittent | 0 | 0       | N/A | N/A |
|                    |           |           | INS only | 424 | 360 | 1.18(1.06-1.31) | 1.17(1.05-1.30) |
|                    |           |           | ICS     | 206 | 242 | 0.85(0.43-1.68) | N/A         |
|                    |           |           | OCS     | 625 | 792 | 0.79(0.61-1.03) | N/A         |
|                    |           |           | ICS & OCS | 352 | 333 | 1.06(0.47-2.38) | N/A         |
| Nasal Perforation  | sub-chronic | 0 | 0       | N/A | N/A |
|                    |           |           | INS only | 180 | 190 | 0.95(0.44-2.02) | N/A         |
|                    |           |           | ICS     | 0   | 180 | N/A       | N/A         |
| Nasal Perforation  | chronic   | 0 | 0       | N/A | N/A |
|                    |           |           | INS only | 0   | 0   | N/A       | N/A         |
|                    |           |           | ICS     | 0   | 0   | N/A       | N/A         |
|                    |           |           | OCS     | 0   | 0   | N/A       | N/A         |
|                    |           |           | ICS & OCS | 0  | 0   | N/A       | N/A         |

† Indicates a significant difference compared to the intermittent group.
| Condition | Frequency | Minimum | Maximum | Lower | Upper |
|-----------|-----------|---------|---------|-------|-------|
| Osteoporosis | chronic | INS only | 14 | 46 | 2.45(0.41-14.6) | N/A |
| ICS & OCS | 0 | 0 | N/A | N/A |
| sub-chronic | INS only | 15 | 43 | 0.36(0.04-3.21) | N/A |
| ICS | 0 | 83 | N/A | N/A |
| OCS | 0 | 0 | N/A | N/A |
| ICS & OCS | 0 | 0 | N/A | N/A |
| sub-chronic | INS only | 1 | 45 | N/A | N/A |
| ICS | 0 | 0 | N/A | N/A |
| OCS | 0 | 0 | N/A | N/A |
| ICS & OCS | 0 | 0 | N/A | N/A |
| Sinusitis | intermittent | INS only | 5,123 | 4,606 | 1.11(1.07-1.15) | 1.11(1.07-1.15) |
| ICS | 1,985 | 2,188 | 0.91(0.70-1.17) | N/A |
| OCS | 3,925 | 3,771 | 1.04(0.91-1.20) | N/A |
| ICS & OCS | 1,886 | 1,913 | 0.99(0.65-1.49) | N/A |
| chronic | INS only | 1,262 | 1,246 | 1.01(0.72-1.43) | N/A |
| ICS | 565 | 1,616 | 0.35(0.10-1.23) | N/A |
| OCS | 924 | 698 | 1.33(0.43-4.11) | N/A |
| ICS & OCS | 1,847 | 2,147 | 0.86(0.31-2.37) | N/A |
| Abscess | intermittent | INS only | 1,333 | 1,142 | 1.17(1.10-1.24) | 1.16(1.08-1.23) |
| ICS | 968 | 803 | 1.21(0.85-1.71) | N/A |
| OCS | 1,362 | 1,447 | 0.94(0.77-1.15) | N/A |
| ICS & OCS | 745 | 869 | 0.86(0.49-1.49) | N/A |
| sub-chronic | INS only | 518 | 557 | 0.93(0.59-1.47) | N/A |
| Condition | Initial | Complete | Mean (Range) | Mean (Range) |
|-----------|---------|----------|--------------|--------------|
| Cellulitis | | | | |
| Chronic | INS only | 334 | 152 | 2.20 (0.76-6.33) | N/A |
| | ICS | 396 | 0 | N/A | N/A |
| | OCS | 598 | 468 | 1.28 (0.29-5.71) | N/A |
| | ICS & OCS | 685 | 314 | 2.18 (0.31-15.5) | N/A |
| Intermittent | INS only | 21 | 22 | 0.94 (0.60-1.48) | 0.94 (0.60-1.49) |
| | ICS | 30 | 40 | 0.75 (0.14-4.08) | N/A |
| | OCS | 20 | 36 | 0.56 (0.14-2.15) | N/A |
| | ICS & OCS | 0 | 45 | N/A | N/A |
| Sub-chronic | INS only | 0 | 11 | N/A | N/A |
| | ICS | 0 | 0 | N/A | N/A |
| | OCS | 0 | 0 | N/A | N/A |
| | ICS & OCS | 0 | 0 | N/A | N/A |
| Chronic | INS only | 14 | 10 | 1.47 (0.79-2.70) | 1.67 (0.90-3.09) |
| | ICS | 60 | 0 | N/A | N/A |
| | OCS | 27 | 5 | 5.19 (0.58-46.5) | N/A |
| | ICS & OCS | 0 | 0 | N/A | N/A |
| Empyema | | | | |
| Intermittent | INS only | 0 | 11 | N/A | N/A |
| | ICS | 0 | 0 | N/A | N/A |
| | OCS | 0 | 0 | N/A | N/A |
| | ICS & OCS | 0 | 0 | N/A | N/A |
| Sub-chronic | INS only | 0 | 11 | N/A | N/A |
| | ICS | 0 | 0 | N/A | N/A |
| | OCS | 0 | 0 | N/A | N/A |
| | ICS & OCS | 0 | 0 | N/A | N/A |
| Chronic | INS only | 0 | 0 | N/A | N/A |
| | ICS | 373 | 0 | N/A | N/A |
| | OCS | 0 | 0 | N/A | N/A |
| | ICS & OCS | 0 | 0 | N/A | N/A |
| Encephalitis | | | | |
| Intermittent | INS only | 3 | 1 | 2.33 (0.56-9.73) | 2.30 (0.55-9.71) |
| | ICS | 0 | 0 | N/A | N/A |
| | OCS | 0 | 0 | N/A | N/A |
| | ICS & OCS | 0 | 0 | N/A | N/A |
### Conclusion

This extensive analysis of very large patient cohorts of FP and other INS has allowed a “real-world” evaluation of events historically associated with corticosteroid exposure. Although the vast majority of patients had intermittent exposure as one dispensing of FP or other INS, results suggested a somewhat higher rate of a few outcomes in the FP-exposed group. Rates of five of the thirteen outcomes assessed were statistically elevated in the intermittent user FP versus other INS cohorts; three were found to have rate ratios between 1.1 and 1.2 (nasal septum perforation, sinusitis, and abscess), indicating marginal clinical impact. Hypercorticism and empyema occurred twice as often in FP patients as compared to other INS patients. Of note, when patients taking concomitant corticosteroids were removed from the analyses of hypercorticism and empyema, the statistical difference between FP and other INS groups dissipated suggesting potential confounding by concomitant corticosteroid use. In contrast to these findings, FP patients were less likely to have a cataract diagnosis than other INS patients. Rates of the seven other incident outcomes evaluated (adrenal insufficiency, fracture, glaucoma, osteoporosis, cellulitis, encephalitis, and meningitis) were not found to be statistically different between the FP and INS cohorts.

### Publications

Motsko SP, Corrao MA, Vendiola RM, Davis KJ, Goehring EL, Jones, JK. 2006. Risk of adverse effects with fluticasone propionate as compared to other intranasal steroids [abstract]. In: 22nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management; 2006 Aug 24-27; Lisbon, Portugal. Bethesda (MD): International Society for Pharmacoepidemiology. 429.

### GSK Medicine:
Fluticasone propionate, beclometasone dipropionate (class level only)

### Study No.:
WWE111983/WE50002

### Title:
An Epidemiological Study of Steroid-Related Outcomes in Users of Fluticasone Propionate Nasal Spray in the
### General Practice Research Database (GPRD)

#### Rationale:
The study was undertaken as part of a multifaceted epidemiological program to evaluate the utilization, safety and outcomes associated with prescription use of intranasal fluticasone propionate (FP).

#### Objectives:
To compare the demographic and clinical characteristics (comorbidities) of Flixonase to other INS users, to determine the rate of specific events of concern among patients with intermittent, sub-chronic and chronic Flixonase use episodes, compared to patients with intermittent, sub-chronic and chronic use episodes of other INS and to assess potential effect modifiers of the association between INS use and events by performing stratified analyses.

#### Indication:
Management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older

#### Study Investigators/Centers: N/A

### Research Methods

#### Data Source:
The General Practice Research Database (GPRD), owned by the Medicines Control Agency in the United Kingdom, comprises the entire computerised medical records of a sample of GPs in the country. All members of the population are registered with a single practice, which centralises the medical information not only from GPs themselves but also from specialist referrals and hospital attendance. This study is based on data from about a 6% sample of the UK population. Data recorded in the GPRD included 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 for diseases that are cross-referenced to the International Classification of Diseases (ICD-8).

#### Study Population:
Patient records dated from January 1990 to January 2002 were used to develop the overall study cohort. The cohort was composed of the following patients: (1) All patients with at least one prescription for Flixonase and (2) a random sample of patients having at least one claim for an INS other than Flixonase. Depending on study group, the index date was defined as the first Flixonase prescription or the first INS prescription (other than Flixonase).

The following patients were excluded from the study cohort:

**Patient-level exclusion**
- Patients with less than 180 days of continuous eligibility before index date
- Patients younger than four years of age at index date
- Patients older than 85 years of age at index date

**Episode-level exclusion**
- When patient history was divided into Flixonase or other INS use episodes, patients with fewer than 120 days of eligibility after the last prescription in the episode

#### Study Exposures, Outcomes:
The following incident outcomes were investigated in the cohorts: cataracts, glaucoma, nasal septum perforation, hypercorticism, adrenal insufficiency, fractures (limited to hip, wrist and vertebral) as proxies for osteoporosis, otitis media, sinusitis and infectious complications of sinusitis. The study evaluated outcomes in patients exposed to Flixonase and other INSs. For the purpose of the descriptive analyses (patient-level analyses), "continuous" Flixonase or other INS exposure were defined as at least four similar prescriptions (four Flixonase or four other INS). The gap between prescription dates could be no longer than 60 days (fill date to fill date).

Flixonase and other INS exposure episodes were identified within all eligible patient histories:
- Intermittent exposure episode - Series of fewer than four (1, 2 or 3) sequential prescriptions for the same drug with gaps of no more than 60 days between any two prescriptions.
- Sub-chronic use episode - Series of at least four and not more than eight sequential prescription s for the same drug with gaps of no more than 60 days between any two prescriptions.
- Chronic use episode - Series of at least nine sequential prescriptions for the same drug and gaps of no more than 60 days between any two prescriptions. A span of at least 180 days must occur between the first and last prescriptions.

#### Data Analysis:
Patients in the Flixonase, other INS and rhinitis cohorts were compared on the basis of the following characteristics: sex, age groups – 4-12, 13-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70+ years and common co-morbidities. The subpopulation of those patients with continuous Flixonase or other INS use greater than or equal to 120 days was
stratified for the analysis described above.

To analyze events, episodes were created within each patient’s history. Episodes of Flixonase or other INS exposure were defined as any series of prescriptions filled within 60 days of one another. A break of more than 60 days constituted a separate episode. Observation periods to capture incident events began with the first prescription in the episode and terminate 120 days (30 days to complete dose plus a 90 day observance tail) after the last prescription date. For the rhinitis cohort with no INS exposure, the observation period began with the rhinitis diagnosis and terminate at end of study period or end of patient’s eligibility, which ever occurred first. Person-time exposure accumulated from the episode index date to an incident event diagnosis date or 60 days after last prescription date within that series, whichever occurred first.

Incidence rates and rate ratios with 95% confidence intervals were calculated for events in the intermittent, sub-chronic and chronic Flixonase and other INS episode groups. Each event (or event group) was analyzed separately. Patients with an event of interest 180 days prior to patients’ entry into the cohort or any time prior to an episode index date were automatically excluded from the analysis of that event. This exclusion criterion was applied to rule out prevalent conditions.

In order to assess potential effect modifiers of the association between INS use and events, analyses were stratified by comorbid disease (type II diabetes, HIV, asthma and sinusitis), concomitant oral and inhaled corticosteroid use and age group.

To be included in the analysis, comorbid conditions must have been diagnosed prior to the episode index date. The dose and duration of concomitant drug use were also examined. For concomitant steroid use, dose and duration of continuous use were measured from the latest overlap with Flixonase or other INS use, backwards to the first prescription in the OCS/ICS series. OCS/ICS prescription series was deemed continuous if less than 120-day gap elapses between prescriptions. ICS doses were standardized by beclomethasone equivalents. Cumulative exposure to ICS was defined as total number of months at low, medium, or high dose as defined in the GINA/NHLBI asthma treatment guidelines. OCS doses were standardized by prednisone equivalents.

**Study Results:** Overall, allergic rhinitis among Flixonase users appeared more severe than among all INS users, according to the number of prevalent conditions in year prior to the index date. WE50002, An Epidemiological Study of Steroid-Related Outcomes in Users of Fluticasone Propionate Nasal Spray in the General Practice Research Database (GPRD) 1990-2002 was initiated in Q4 2002 to provide background information as part of an evaluation process for Flixonase [fluticasone propionate nasal spray (FPNS)] as an over-the-counter (OTC) product in the United States (US). WE50002 was an observational study with parallel study design to a US healthcare insurance claims study, WE50001. The purpose of these retrospective cohort studies was to determine the rates of steroid-related adverse events in a FPNS patient cohort (n=62,380 in the GPRD study and n=52,870 in the US study), compared to an all other intranasal steroids (INS) patient cohort (n=270,802 in the GPRD study and n=73,743 in the US study). Incidence rates and rate ratios with 95% confidence intervals were calculated for events in intermittent, sub-chronic and chronic INS use episodes within each patient cohort. The design of WE50002 included a number of specific outcomes of interest, pertinent to the class of corticosteroids in an OTC environment. Outcomes included the following: cataracts, glaucoma, nasal septum perforation, hypercorticism, adrenal insufficiency, fractures (limited to hip, wrist and vertebral) as proxies for osteoporosis, acute otitis media, chronic otitis media, acute sinusitis, chronic sinusitis, infectious complications of sinusitis [cellulitis (periorbital), empyema (maxillary), abscess (brain), meningitis and encephalitis].

In WE50002, crude hazard ratios comparing FPNS with other INS suggested an increased risk of nasal septum perforation (n=841, crude HR 1.39 [95% CI 1.18, 1.63]), osteoporosis (n=221, crude HR 1.66 [95% CI 1.23, 2.23]), chronic sinusitis (n=984, crude HR 1.80 [95% CI 1.57, 2.07]), diabetes (n=353, crude HR 1.19 [95% CI 0.92, 1.53]) and abscess (n=35, crude HR 1.55 [95% CI 0.73, 3.31]) associated with FPNS use. The final adjusted hazard ratios for these events were all less than 1.50, suggesting weak associations with FPNS. The reduction from crude risks to adjusted relative risks in multivariate Cox models suggested that some confounding was removed, however concern remained about residual confounding by indication/severity given the limited detailed information available for inclusion in these analyses. For instance, it is possible that restriction of newer or more expensive therapies in the UK health system to patients who do not respond favourably to less expensive or older medicines caused channelling or confounding by severity to occur in UK GPRD study.
There were no differences of clinical significance in rates of outcomes of interest between patients receiving FP and other INS in WE50002; however in order to obtain a clearer understanding of the potential for residual confounding in the GPRD study, WE50001- An Epidemiological Study of Overall Patterns of Use & Outcomes in Users of Fluticasone Propionate (Flonase) Nasal Spray was conducted in a large US healthcare claims database. Designed in parallel to WE50002, the US study utilized preliminary findings from WE50002 to select additional key variables for appropriately modelling each outcome of interest. While age, sex, acute sinusitis, oral corticosteroids (OCS), inhaled corticosteroids (ICS), antihistamine prescriptions, nasal polyps, and number of visits to a general practitioner in the prior 12 months were included in the WE50002 models, the US database study allowed a more granular characterization of patients’ risk profiles including dispensed medications, comorbid diagnoses, utilization and procedure data, and consequently allowed for a better control of potential confounding factors. The US study results were consistent with the anticipated risk profile for an INS and did not raise any new safety signals.

In WE50002, the GPRD study, the adjusted hazard ratio for nasal septum perforation was 1.41 (95% CI 1.21, 1.67). In the companion US study, WE50001, covariates evaluated for inclusion in the multivariate model were age, gender, past and concurrent OCS or ICS, interacting drugs, nasal trauma, neoplastic causes, sarcoidosis, and Wegener granulomatosis. Due to the stepwise regression analysis and/or the lack of an association with an endpoint event several of these variables were removed (neoplastic causes, sarcoidosis, and Wegener granulomatosis). All concurrent corticosteroid variables, recent past use of OCS and OCS/ICS, nasal trauma, age, and gender were found to be statistically significant in the multivariate model. The adjusted risk ratio for nasal septum perforation in the US study was 1.10 (95% CI, 1.00 - 1.22), lower than the risk estimate observed in the GPRD study.

While sinusitis was also associated with FPNS as compared with other INS in WE50001, the relative risk was lower (1.10; 95% CI, 1.07 - 1.14 in the US study versus 1.40; 95% CI, 1.23, 1.63 in the GPRD study). In the GPRD study, the observed association suggested FPNS was prescribed more often than other INS after multiple acute events (confounding by severity). In the US study, the list of covariates evaluated for inclusion in the multivariate model was subsequently extended to include age, gender, past and concurrent steroid use, interacting drugs, asthma, cystic fibrosis, Kartagener’s, immune system disorders, chemotherapy, upper repertory infections, immunosuppressants, HIV/AIDS, region, and season. Age, gender, region, season, asthma, upper respiratory infections, “recent past” ICS use, concurrent corticosteroid use (all categories), itraconazole, and ketoconazole were all found to be independent risk factors in the multivariate model.

Abscess was also statistically associated with FPNS as compared with other INS in WE50001; however the relative risk was lower (1.13; 95% CI, 1.07 - 1.20 in the US study versus 1.40; 95% CI 0.65, 3.02 in the GPRD study). Covariates evaluated for inclusion in the multivariate model assessing abscess in the US study were age, gender, past and concurrent steroid use, interacting drugs, asthma, cystic fibrosis, Kartagener’s, immune system disorders, chemotherapy, upper repertory infections, immunosuppressants, HIV/AIDS, region, and season. Age, gender, region, season, upper respiratory infections, “recent past” ICS/ICS use, concurrent ICS and concurrent ICS/ICS were found to be statistically significant in the multivariate model.

The rate of osteoporosis did not differ between the FPNS and other INS cohorts (RR, 1.08; 95% CI, 0.77 – 1.52) in the US study. The US study found additional covariates were associated in the multivariate model for osteoporosis, including age, gender, thiazides, estrogen, bisphosphonates, OCS “recent past,” ICS/ICS “remote past,” and concurrent ICS/OCS use. Without the assessment of these additional covariates in the GPRD study, the adjusted relative risk was 1.48 (95% CI 1.09, 1.99). Furthermore, osteoporosis incidence stratified by intermittent, sub-chronic and chronic FPNS and other INS use was highest in the sub-chronic, instead of the chronic, user groups for both FPNS and INS. These finding are counter to biological plausibility for an association between INS use and osteoporosis which has an established corticosteroid dose-response relationship in prior published research.

Diabetes was not assessed in WE50001. Since preliminary observations from WE50002 were used to inform WE50001 and the US study better controlled for important confounders, the results from the latter study (WE50001) have been considered to be the most definitive of this companion/parallel study pair. Furthermore, because this was a retrospective observational study evaluating multiple events of interest with simple cohort design and treatments were not randomised, the conclusions from this study are best suited for hypothesis generation. These data must be considered together with results from other observational studies and those from randomised clinical studies of longer duration, in order to obtain a clearer understanding of the long-term effects of intranasal corticosteroids on risk of the aforementioned outcomes. There were no differences of clinical significance in rates of outcomes of interest between patients receiving FP and other INS in WE50002 or WE50001. Taken together, the study results were consistent with the anticipated risk profile for an INS and did not raise any new safety signals.
**Limitations**: Because this was a retrospective observational study and treatments were not randomised, the conclusions from this study are best suited for hypothesis generation. These data should be considered together with results from other observational studies and those from randomised clinical studies of longer duration in order to obtain a clearer understanding of the long-term effects of intranasal corticosteroids on risk of the aforementioned outcomes. The conduct and results of this study were used to inform WE50001- An Epidemiological Study of Overall Patterns of Use & Outcomes in Users of Fluticasone Propionate (Fionase) Nasal Spray.

Lifetime data on corticosteroid use were not available, as information was restricted to the period of GPRD data collection. Some patients may have received ICS or OCS before data collection and discontinued use before their pharmacy record was included in GPRD. Misclassification of drug exposure during the study period was also possible. The GPRD provided information on prescribed rather than dispensed prescriptions. As a result it is possible that patients may have been prescribed medication that was never used or used less or more frequently than prescribed. Audits of the GPRD have demonstrated a relatively high concordance of dispensing to prescription.

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