### Title
COMPARATIVE EFFECTIVENESS AND SAFETY OF SALBUTAMOL STERINEBS® VS. VENTOLIN NEBULES® IN COPD PATIENTS.

### Subtitle
Historic cohort, UK database study comparing effectiveness and safety of nebulised medication labelled by TEVA Ltd (Salbutamol SteriNebs®) against the originator product (Ventolin Nebules®), in patients who received a diagnosis for COPD

### Protocol version identifier
v03

### Active substance
Salbutamol/Albuterol

### Medicinal product
Salbutamol Sterinebs® (2.5 and 5.0mg/2.5ml)

### Product code
231-10-FN0032 (2.5mg/2.5ml)
231-10-FN0031 (5.0mg/2.5ml)

### Marketing authorization holder
Norton Healthcare Limited T/A IVAX Pharmaceuticals
Ridings Point
Whistler Drive
Castleford
West Yorkshire
WF10 5HX
United Kingdom

### Marketing authorisation number
PL 00530/0690 (2.5mg/2.5ml)
PL 00530/0693 (5.0mg/2.5ml)

### Research questions and objectives
To examine if nebulised medication labelled by TEVA Ltd (Salbutamol SteriNebs®) is non-inferior to (at least as effective and safe as) the originator product (Ventolin Nebules®)

### Country of study
UK

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1. BACKGROUND AND RATIONALE

Teva Ltd is a global company ranking among the 10 top pharmaceutical companies in the world. Headquartered in Israel, Teva is active in 60 countries, with over 46,400 dedicated employees worldwide. The company is now looking to launch 3 different nebuliser products in China: Budesonide, Salbutamol and Ipratropium Bromide/Albuterol SteriNebs®. This protocol focuses on Salbutamol SteriNebs®.

Salbutamol SteriNebs® is currently marketed in Europe in Denmark, Belgium, Greece, France, Netherlands, Norway, Portugal, Poland and United Kingdom (UK) and is the generic product of Ventolin Nebules®, which is marketed worldwide, including China.

The active ingredient is Salbutamol Sulphate, a derivative of Salbutamol, which is a selective β2 adrenoreceptor agonist providing short-acting broncho-dilation with a fast onset in reversible airways obstruction. It is prescribed for the routine management of chronic bronchospasm unresponsive to conventional therapy, as well as for the treatment of acute severe asthma.

In order to support a clinical trial waiver for marketing Salbutamol SteriNebs® in China, Teva will provide recent data demonstrating their product is not inferior to the originator Ventolin Nebules®. To accomplish this, an historic, cohort, data-base study will be conducted comparing effectiveness and safety of the usage of the two products in UK, where Salbutamol Sterinebs® is on the market since May 1992 (2.5mg/2.5ml formulation) and January 1993 (5mg/2.5ml formulation). A regulatory standard protocol, together with the completed analysis will be provided for the submission to Chinese regulators.

2. AIM AND OBJECTIVES

The aim of this study is to compare Salbutamol SteriNebs® with its originator, Ventolin Nebules®. The primary objective is to assess whether effectiveness (in terms of COPD exacerbations) of Salbutamol SteriNebs® is non-inferior to that of Ventolin Nebules®. The secondary objective is to compare safety of Salbutamol SteriNebs® vs Ventolin Nebules®. In order to evaluate the regular usage of the two drugs, this study will primarily look at COPD patients, however, patients with comorbid asthma will not be excluded.
3. DATA SOURCE AND EXTRACTION

This study will use the Optimum Patient Care Research Database (OPCRD) (1), approved by Trent Multi Centre Research Ethics Committee for clinical research use and comprising anonymised data collected from 430 practices in UK. Two types of anonymised patient data are typically included in this database:

- Routine clinical data: a dedicated software interfaces with primary care practice management systems and extracts anonymised, patient-level diagnostic, clinical and prescribing information.
- Patient reported outcomes: Eligible respiratory patients (e.g. those with diagnoses and/or in receipt of prescriptions for obstructive lung disease and approved for participation by the general practitioner) are invited to complete validated disease assessment questionnaires to capture patient reported data on disease status and (where present) possible reasons for sub-optimal control/disease status.

In particular, the data available from OPCRD includes:

- Demographics (including age and sex)
- Medical symptoms, signs and diagnoses
- Therapy (medicines, vaccines, devices)
- Treatment outcomes
- Patient reported outcomes
- Events leading to withdrawal of treatment
- Referrals to hospitals or specialists
- Laboratory tests, pathology results
- Lifestyle factors (height, weight, BMI, smoking and alcohol consumption)
- Patient registration, practice and consultation details

In order to ensure appropriate numbers of patients to be included in the study, OPCRD data will be supplemented with data from the Clinical Practice Research Datalink (CPRD) (2), which is the computerised primary care database funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA) containing anonymous longitudinal data extracted from approximately 600 practices throughout the UK.
Data will be obtained from each database for the final analysis using appropriate data extraction algorithms. Obtained data will be pooled after local extraction, validation and data cleaning. Duplicate practices will be identified and will not be included.

4. RESEARCH METHODS

4.1 Study products
- Reference Therapy: VENTOLIN NEBULES®

Originator product consisting of a solution for inhalation via a nebulizer containing the short-acting β2-adrenergic agonist (SABA) salbutamol sulfate. Two dose strengths are available in single-dose ampules: 2.5mg and 5.0mg per 2.5ml.

- Investigational Product: SALBUTAMOL STERINEBS®

Generic product of Ventolin Nebules®. It is a solution for inhalation via a nebulizer containing the SABA salbutamol sulfate. It is also available in two dose strengths: 2.5mg and 5.0mg per 2.5ml.

4.2 Study period
In order to include as many patients as possible, the study period will cover 2 years within a maximum period from May 1991 (one-year before launch of Salbutamol SteriNebs in UK) up to date of last available data.

4.3 Study design
This study will be designed as a matched historic, cohort, database study consisting of a baseline period, an index prescription date (IPD) and an outcome period (Fig.1).

The baseline period is 1-year period before and including IPD1 and is intended for patient characterization and confounder definition. The IPD is defined as the date (day/month/year) at which:

(1) CHANGE SUB-COHORT: COPD patients who were on Ventolin Nebules® in baseline changed to Salbutamol SteriNebs® (Patients receive ≥ 1 prescription).

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1 Except for therapy prescribed at IPD (which is included in the outcome).
(2) CONTINUING SUB-COHORT: COPD patients who were on Ventolin Nebules® in baseline received ≥ 1 continued prescription for Ventolin Nebules®.

(3) INITIATION SUB-COHORTS: COPD patients who were not on SABA nebulisers in baseline initiated on either Ventolin Nebules® or Salbutamol SteriNebs®.

Change and initiation sub-cohorts for Salbutamol SteriNebs® will be combined to form the “Salbutamol SteriNebs® treatment cohort” and compared to “Ventolin Nebules® treatment cohort” consisting of a combination of continuing and initiation sub-cohorts for Ventolin Nebules®. Matching will be performed between the two initiation sub-cohorts and between the change and continuing sub-cohorts to ensure comparison of homogeneous groups of patients. A sub-analysis comparing the two initiation sub-cohorts only will also be performed as a sensitivity analysis to confirm the main results. Effectiveness outcomes over the one-year outcome period following IPD will be compared between the treatments.

Figure 1: Study design

The outcome period is 1-year period following IPD and will be used to compare drug effectiveness and safety.
In order to ensure adequate number of patients in the cohorts, we will include patients that after 1-year may change back from Salbutamol SteriNebs® to Ventolin Nebules® or vice versa. Therefore patients may be included more than once with different prescription dates if they satisfy the inclusion/exclusion criteria, however only unique patients will be analysed after matching (details below).

One-year time periods for outcome and baseline are deemed necessary to record any measurable change in variables, and also to allow for seasonal changes in respiratory disease and its related conditions.

### 4.4 Study population

People who have been diagnosed at any time with COPD (based on NHS Read codes reported in Annex 1), including patients who also received a diagnosis for asthma, will be included in the analysis if they meet the following criteria:

**Inclusion criteria**

- Aged ≥40 years at IPD
- Change cohort: ≥1 prescription for Ventolin Nebules® in baseline (1 year prior to IPD) and ≥1 prescriptions for Salbutamol SteriNebs® at IPD
- Continuing cohort: ≥1 prescription for Ventolin Nebules® during baseline (1 year prior to IPD) and ≥1 continued prescription for Ventolin Nebules® at IPD
- Initiation cohorts: no prescriptions for SABA nebulisers in baseline (1 year prior to IPD) and ≥1 prescription for either Salbutamol SteriNebs® or Ventolin Nebules® at IPD
- At least two years of continuous data (1 year prior and 1 year post IPD)

**Exclusion criteria**

- Any other chronic respiratory disease other than asthma and COPD at any time
- Patients received prescriptions for other SABA nebulisers besides Salbutamol SteriNebs® or Ventolin Nebules® in the baseline period (1 year prior to IPD)

### 5. VARIABLES

#### 5.1 Primary outcome

Primary outcome of this study is “effectiveness”, evaluated in terms of:

- Severe COPD exacerbations (hospitalisations) in the outcome period
- Moderate and severe COPD exacerbations in the outcome period

Whereby:

**Severe COPD exacerbations (hospitalisations)** is defined as:

- Coded admission to Emergency Department or Hospital for COPD OR

- Recorded hospitalisation admission on the same day as a lower respiratory consultation\(^2\) (excluding where the only lower respiratory code recorded on that day was for a lung function test).

**Moderate and severe COPD exacerbations** is defined as\(^3\):  

- Severe COPD exacerbation (hospitalisation) OR

- An acute course of oral steroids\(^4\) prescribed with a lower respiratory consultation OR

- Antibiotics prescribed with a lower respiratory consultation

### 5.2 Secondary (exploratory) outcome

Secondary outcome of this study is “**safety**”, evaluated in terms of Adverse Events (AEs). Unique AEs are not identified in the database (OPCRD or CPRD). Instead pre-defined adverse terms can be identified and coded according to Medical Dictionary for Regulatory Activities (MedDRA) standards. These will include AEs known to be related to Salbutamol SteriNeb\(^{®}\) and Ventolin Nebules\(^{®}\), as specified in their respective summary of product characteristics.

In order to do so, our Read codes will be converted to MedDRA codes and categorised by disease area (e.g. cardiovascular events, renal events) in line with the Read code categorisations detailed in Annex 2.

Data will be extracted on all adverse events, serious or otherwise. Events of particular note include:

- Cardiac events

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\(^2\) Defined as:
- Lower respiratory diagnostic codes (including Asthma, COPD and lower respiratory tract infection (LRTI) Read codes) or asthma/COPD review codes excluding any monitoring letter codes or lung function and/or asthma monitoring AND
- Any additional respiratory examinations, referrals, chest x-rays, or events.

\(^3\) Where ≥1 oral steroid course / hospitalisation / antibiotics prescription occur within 2 weeks of each other, these events will be considered to be the result of the same exacerbation (and will only be counted once).

\(^4\) Defined as:
- All courses that are definitely not maintenance therapy, and/or
- All courses where dosing instructions suggest exacerbation treatment (e.g. 6, 5, 4, 3, 2, 1 reducing, or 30mg as directed), and/or
- All courses with no dosing instructions, but unlikely to be maintenance therapy, with a code for COPD or a lower respiratory event.
- Glaucoma
- Prostatic hypertrophy
- Respiratory adverse events
- Death (serious adverse event)

5.3 Demographics and baseline variables

In order to capture real-world data on the utilisation of Salbutamol SteriNebs® and Ventolin Nebules® in clinical practice, the patients prescribed these therapies will be characterised according to their:

- Age at or nearest to IPD and gender
- Smoking status recorded closest to IPD, if available (patients will be classified as “current smokers”, “ex-smokers” and “non-smokers”)
- BMI, calculated as weight/height² and categorised in standard categories of “underweight” (<18.5), “normal weight” (≥18.5 and <25), “overweight” (≥25 and <30) and “obese” (≥30). Height and weight will be the height and weight measurements taken closest to IPD
- Prior maintenance therapy (maintenance therapy prescribed before IPD)
- Baseline co-medications (presence of a prescription of non-steroidal anti-inflammatory drugs (NSAIDs) and beta-blockers)
- Disease control in the year prior to IPD, defined as:
  - Number of COPD-related exacerbations, as applicable
  - COPD-related hospitalisations (Emergency visits and inpatients admissions)
  - Prescription for acute oral corticosteroids or antibiotics for treating exacerbations
  - Reliever medication usage
- Co-morbidities (presence of co-morbid diagnoses, also using the Charlson Comorbidities Index)
- Prescribed dose and dosing instructions for both drugs at IPD

6. STATISTICS

Analyses will be carried out using SPSS Statistics 21 (IBM SPSS Statistics, UK) and SAS 9.3 (SAS Institute, UK) software.
6.1 Power calculation
A previous RiRL study has reported that 40.8% of COPD patients (2,730 out of 6,687 patients) using Salbutamol inhalers have at least one exacerbation in the period of 1 year after initiation\(^5\). Assuming the proportion in the standard group is 40.8% and an expected difference between the proportions is 0.000, the sample size required to adequately power the study in a two-group large-sample normal approximation, with a one-sided 0.050 significance level is 1,112 for each group. This enables a 90% power to reject the null hypothesis that the investigational and the reference are not equivalent (the difference in proportions is -6% (15% of 40%) or farther from zero in the same direction).

Number of patients potentially available from the two databases are reported in Table 2.

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<td>(TEVA UK Ltd)</td>
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<td>(GlaxoSmithKline plc)</td>
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Table 2: Preliminary numbers for asthma and COPD patients with at least a prescription for the study drugs.

6.2 Exploratory analysis
Prior to the extended statistical analysis, an exploratory analysis of each cohort will be carried out for data validation and to identify potential outliers. The exploratory analysis will also help to investigate possible baseline differences between the two treatment groups in order to evaluate whether the analysis may benefit from matching. Unmatched/matched statistical analyses will be performed using appropriate regression modelling. This robust statistical approach minimizes potential confounding of results by indication or severity. Statistically significant results will be defined as p<0.05 and trends as p<0.10.

\(^5\) Data presented at annual scientific meeting of the American College of Allergy, Asthma and Immunology (ACAAI), November 7-11, 2013, Baltimore, USA.
6.3 Summary statistics
Summary statistics will be produced for all baseline and outcome variables, as a complete
dataset and by treatment groups, including:

(1) Variables measured on the interval/ratio scale:
   - Sample size (n) and percentage non-missing
   - Mean and Variance / Standard Deviation
   - Range (Minimum / Maximum)
   - Median and Inter-quartile Range (25th and 75th percentiles)

(2) Categorical variables:
   - Sample size (n)
   - Range (if applicable)
   - Count and Percentage by category (distribution)

6.4 Comparisons between treatment groups
Treatment groups will be compared using the following tests:

(1) Variables measured on the interval/ratio scale:
   - t-test (normal distribution)
   - Mann Whitney U-test (skewed data)

(2) Categorical variables:
   - Chi square test

6.5 Patient matching
If necessary depending on baseline results, individual patients in the two treatment groups
(i.e. Ventolin Nebules® or Salbutamol SteriNebs®) will be matched to ensure the comparison
of like patients. All the valid records satisfying inclusion and exclusion criteria in the Ventolin
Nebules® study cohort are considered as potential 1:1 matches to Salbutamol SteriNebs®
patients. The final selection of matched patients will ensure that only unique patients are
selected from all cohorts by random methods. Random selection process through SAS
statistical software will be used to avoid selection bias. Patients initiating on Ventolin
Nebules® will be matched with patients initiating on Salbutamol SteriNebs® and patients in
the continuing cohort will be matched with patients in the change cohort.
The matching criteria and matching ratio will be determined once the baseline data are examined. Baseline characterisation will be via demographics and clinical variables (for example age, gender, baseline exacerbations, acute oral steroid use or average daily SABA inhalers use during baseline). Any residual differences between the treatment groups after matching that are considered to be potentially significant (p<0.10) and any variables predictive of the outcome will be adjusted for through further statistical modelling. When variables are co-linear in nature, clinical input will be sought to decide which of those that are co-linear are put into the model.

6.6 Comparisons between effectiveness outcomes (primary analyses)

(1) Severe COPD exacerbations (hospitalisations) rate
Severe COPD exacerbations (hospitalisations) in the outcome period will be compared between treatment groups using a Conditional Poisson regression model. The model will use empirical standard errors (for more conservative confidence interval estimations) and adjustments will be made for potential baseline confounders. The adjusted rate ratio with 95% confidence interval will be reported.

(2) Moderate and severe COPD exacerbations rate
Moderate and severe COPD exacerbation rates in the outcome period will be compared between treatment groups using a conditional Poisson regression model. The model will use empirical standard errors (for more conservative confidence interval estimations) and adjustments will be made for potential baseline confounders. The adjusted rate ratio with 95% confidence interval will be reported.

Baseline characterisation will be used to adjust for confounding factors. Those variables that will be significantly different or show a trend towards a difference (p < 0.10) between the treatment groups at baseline will be included as potential confounding factors. In addition, variables that are found to be predictive (p < 0.05) of the outcome through multivariate analysis will also be considered as potential confounders.

6.7 Comparisons among safety variables (secondary/exploratory analyses)
AEs rates (as total and individual events) in the outcome period will be compared between treatment groups using a conditional Poisson regression model. The model will use empirical standard errors (for more conservative confidence interval estimations), and adjustments will
be made for potential baseline confounders. The adjusted rate ratio with 95% confidence interval will be reported.

A more detailed description of the statistical analysis is reported in the attached statistical analysis plan (SAP).

7. LIMITATIONS OF RESEARCH METHODS
As with all database studies, a number of limitations exists for which it is not possible to adjust (e.g. potential confounding factors with the problem of internal validity).
The methods of adjustment described in the Study Design will be used to address all factors for which it is possible to account for. Given the inherent limitations of database studies, however, the study results need to be viewed in conjunction with those from other studies, in particular randomised controlled trials.

8. PROTECTION OF HUMAN SUBJECTS
The OPC service evaluation combines records-based assessments with patient-reported questionnaire responses to evaluate the effectiveness of the current respiratory service being offered. Due to the sensitive nature of personal medical data, all the researchers involved in this study are aware of ethical and regulatory issues and strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy. The OPCRD and CPRD databases that will be utilised in this study are already used for Pharmacoepidemiological research (3-6) and have a well-developed mechanism to ensure that regulations dealing with ethical use of the data and adequate privacy control are adhered to.
All patient-level data collected by OPC are anonymised at the point of extraction, but clinical records and patient reported outcomes can be cross-referenced through use of unique patient identifiers. Where appropriate, OPC makes recommendations for management changes (in line with best practice respiratory guidelines). All recommendations are returned to the practice for consideration and are only adopted at the discretion of the physician.
Anonymous service evaluation data is held in the OPCRD, which has been granted ethical approval for use in medical research by the Trent Multi-Ethics Research Committee.
9. REGULATORY AND ETHICAL COMPLIANCE
This study was designed and shall be implemented and reported in accordance with the criteria of the “European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study” and follows the ENCePP Code of Conduct (EMA 2014) (7).

10. DISSEMINATION PLAN
This study will be registered with ENCePP with the aim of presenting initial results in poster/oral format at appropriate thoracic conferences. At least one manuscript containing more detailed results and methodology will be submitted to a journal specialising in respiratory medicine. Submission for publications should be made as soon as the analyses are completed and the results are verified. Preferred respiratory congresses and journals will be agreed in discussion with Teva Ltd.

11. STUDY TEAM
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12. REFERENCES
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<td>H582.00</td>
<td>Compensatory emphysema</td>
</tr>
<tr>
<td>Hyu3000</td>
<td>[X]Other emphysema</td>
</tr>
<tr>
<td>Hyu3100</td>
<td>[X]O spcf chron obs pulmon dis</td>
</tr>
<tr>
<td>H32y111</td>
<td>Acute interstitial emphysema</td>
</tr>
<tr>
<td>H32y200</td>
<td>MacLeod's unilateral emphysema</td>
</tr>
<tr>
<td>H32yz00</td>
<td>Other emphysema NOS</td>
</tr>
<tr>
<td>H32yz11</td>
<td>Sawyer - Jones syndrome</td>
</tr>
<tr>
<td>H32z.00</td>
<td>Emphysema NOS</td>
</tr>
</tbody>
</table>
14. ANNEX 2
Medical Dictionary for Regulatory Activities (MedDRA) Read codes categorised by disease area.

<table>
<thead>
<tr>
<th>READ CODE</th>
<th>READ TERM</th>
</tr>
</thead>
<tbody>
<tr>
<td>A....00</td>
<td>Infectious and parasitic diseases</td>
</tr>
<tr>
<td>B....00</td>
<td>Neoplasms</td>
</tr>
<tr>
<td>C....00</td>
<td>Endocrine, nutritional, metabolic and immunity disorders</td>
</tr>
<tr>
<td>D....00</td>
<td>Diseases of blood and blood-forming organs</td>
</tr>
<tr>
<td>E....00</td>
<td>Mental disorders</td>
</tr>
<tr>
<td>F....00</td>
<td>Nervous system and sense organ diseases</td>
</tr>
<tr>
<td>G....00</td>
<td>Circulatory system diseases</td>
</tr>
<tr>
<td>H....00</td>
<td>Respiratory system diseases</td>
</tr>
<tr>
<td>J....00</td>
<td>Digestive system diseases</td>
</tr>
<tr>
<td>K....00</td>
<td>Genitourinary system diseases</td>
</tr>
<tr>
<td>L....00</td>
<td>Complications of pregnancy, childbirth and the puerperium</td>
</tr>
<tr>
<td>M....00</td>
<td>Skin and subcutaneous tissue diseases</td>
</tr>
<tr>
<td>N....00</td>
<td>Musculoskeletal and connective tissue diseases</td>
</tr>
<tr>
<td>P....00</td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>Q....00</td>
<td>Perinatal conditions</td>
</tr>
<tr>
<td>R....00</td>
<td>[D]Symptoms, signs and ill-defined conditions</td>
</tr>
<tr>
<td>S....00</td>
<td>Injury and poisoning</td>
</tr>
<tr>
<td>T....00</td>
<td>Causes of injury and poisoning</td>
</tr>
<tr>
<td>U....00</td>
<td>[X]External causes of morbidity and mortality</td>
</tr>
<tr>
<td>Z....00</td>
<td>Unspecified conditions</td>
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</tbody>
</table>