Title: Real-life effectiveness (and cost impact) evaluation of fixed-dose combination fluticasone propionate/formoterol (Flutiform®) for the management of asthma in a routine UK primary care population – Phase 1

A Research in Real Life Study Protocol developed on behalf of Napp Pharmaceuticals

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Objective

To evaluate the success (and cost impact) of changing real-life asthma patients from fluticasone propionate / salmeterol (Seretide®; FP/SAL) to fluticasone propionate / formoterol (Flutiform®; FP/FOR) and to evaluate the comparative effectiveness of FP/FOR, relative to FP/SAL, in real-life asthma patients:

(a) Initiating FDC inhaled corticosteroid/long-acting beta$_2$-agonist (ICS/LABA) therapy[a] as FP/FOR or FP/SAL; or,
(b) Either changing from current FDC FP/SAL to FP/FOR at the same or lower BDP-equivalent ICS dose, or continuing on current FDC FP/SAL.

Background

Asthma is one of the most common chronic diseases, with an estimated 300 million sufferers worldwide [1]. In addition to its effect on quality of life (of both patients and caregivers) it represents a considerable financial burden to society, through direct medication costs and those arising from emergency treatment [2]. A recent European study suggested that over 50% of patients with asthma are sub-optimally controlled [3]. In patients whose asthma is not adequately controlled by ICS alone, the current Global Initiative for Asthma (GINA) guidelines recommend the addition of a LABA as a valid step-up option [4]. The combination of ICS and LABA provides both anti-inflammatory and bronchodilatory effects. Data suggest that combination ICS/LABA therapy is most effective when delivered as a *fixed dose combination* (FDC) inhaler, probably due to simplicity of dosing and improved patient adherence [5].

Optimising medication adherence is a challenge in chronic disease management, but it is believed that the addition of LABA to ICS may improve adherence, in part, because the bronchodilator's effect may afford symptom relief and enhance patients' perception of their treatment's efficacy. It is hypothesised that the faster the onset of action of the LABA in a FDC, the more rapid the symptom relief the patient may experience and, hence, the greater their perception of medication benefit. To this end, combining the anti-inflammatory effects of FP with the rapid-onset bronchodilatory effects of formoterol [6], as used in FP/FOR, may provide more rapid symptom relief than combining FP with the slower-acting LABA salmeterol (i.e. as in Seretide). A recent study demonstrated that up to 40% of the patients were found activating an empty or near empty MDI resulting in sub-optimal therapy [7]. Hence, a dose counter like in Flutiform® will be advantageous in improving patient compliance. In addition, fine particle size was found to have a positive impact on lung deposition [8]. On the same line of real-life benefits, Flutiform® was found to provide a consistent fine particle fraction of approximately 40% of the delivered dose [9, 10]. These practical designs of FP/FOR together with the rapid symptom relief of formoterol may add to better asthma management.

This hypothesis is supported by early randomized controlled trial (RCT) data that suggest FP/FOR is as effective as FP/SAL, but achieves more rapid bronchodilation [11, 12]. Further longitudinal studies are required with FP/FOR to ascertain the implications of this rapid-

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[a] Stepping-up from ICS maintenance therapy

action bronchodilation in terms of improved adherence and effectiveness when used in real-life clinical practice.

Hypotheses

Owing to the hypothesised enhanced adherence to their FDC ICS/LABA due to the fast action of formoterol, patients prescribed FP/FOR will achieve outcomes at least as good as patients prescribed FDC FP/SAL. The clinical benefit of improved adherence and overall asthma control management afforded by FP/FOR may also be discernible in terms of reduced overall asthma-related costs.

Data Source

Optimum Patient Care Research Database

The Optimum Patient Care Research Database (OPCRD) comprises anonymised data extracted from practices receiving Optimum Patient Care's chronic respiratory service evaluation. Two types of anonymised patient data are typically collected:

(i) Routine clinical data: Optimum Patient Care (OPC) software interfaces with primary care practice management systems and extracts anonymised, patient-level diagnostic, clinical and prescribing information.

(ii) 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 practice GP) 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.

See Appendix 1 for further information regarding the creation of the study dataset.

Study Design

Methodology
This will be a matched retrospective, observational database study with a baseline and outcome period designed to evaluate the effectiveness (absolute and compared with FDC FP/SAL MDI) and cost impact of initiating FDC ICS/LABA as FP/FOR or changing to FP/FOR from existing FP/SAL MDI.

Study periods
The study period will run from one year before the UK FP/FOR launch through to 6 months post launch, comprising a baseline period, an index prescription date and an outcome period.

Index prescription date

Change cohort: For those patients changing to FP/FOR from existing FP/SAL MDI the IPD will be the date for their first FP/FOR prescription. For patients in the control arm, i.e. those who continue on FP/SAL MDI therapy, the IPD will be defined as the date of prescription issuance closest to the IPD of their matched FP/FOR counterparts.

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Baseline

The **baseline period** will be the one-year period immediately prior to the IPD, during which patients will be characterised in terms of demography, clinical characteristics and asthma severity.

Outcome Periods

Outcomes will be evaluated for **Phase 1** at six months immediately post IPD at which point FP/FOR treatment success will be evaluated for patients who have changed from FP/SAL to FP/FOR therapy (see Outcomes Section for definition of "success").

## Exposures and Outcomes

General

- FP/FOR patients receiving prescriptions for any of the following formulations twice-daily will be eligible for inclusion: 100:10µg, 250:10µg and 500:20µg.
- FP/SAL patients will be eligible if they are receiving therapy via either pressurised metered-dose inhaler [pMDI; Evohaler®]

Outcome periods

Phase 1: Evaluated at one-year post UK FP/FOR launch in patients who, at IPD, change from existing FDC ICS/LABA therapy to FP/FOR and in whom there is ≥6-months of clinical data available post IPD. There is the opportunity to explore these different changes:

        a) FP/SAL (pMDI) → FP/FOR

        b) FP/SAL (pMDI) → FP/SAL (pMDI)

6-month FP/FOR switch success evaluation
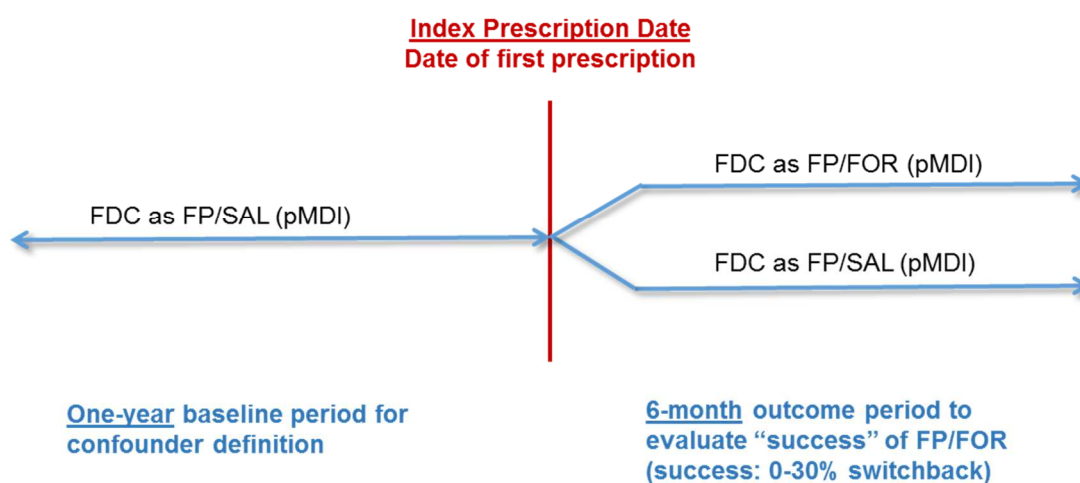
Study population

Inclusion criteria:

To be included in the study dataset, patients must also meet the following inclusion criteria:

(i) Aged: 12–80 years
(ii) Evidence of active asthma, defined as a diagnostic code and/or ≥2 prescriptions for asthma therapy during the baseline year. For patients included in the matched 12-month comparative evaluation:
    • **Initiation cohort:** patients must have received ≥1 ICS prescription during baseline.
    • **FDC change cohort:** patients must have received ≥1 FDC prescription during baseline.
(iii) **Evidence of continued asthma treatment** *in patients evaluated 12-months post IPD only*: ≥2 FP/FOR prescriptions during the outcome period
(iv) **Continuous records:**
    • **For patients evaluated over the 6-month outcome period:** at least one year of baseline data and at least 6 months of outcome data.
    • **For patients evaluated over the 12-month outcome periods:** at least one year of baseline data and at least one year of outcome data.
(v) All FP/FOR patients must be registered at practices considered to have a policy of FP/FOR adoption or wholesale change. Such practices will be identified as those at which ≥5 patients initiate on FP/FOR or change from existing FDC ICS/LABA (any) therapy to FP/FOR within a three-month period.

Exclusion criteria:

Patients will be excluded if they:

(i) Have a diagnosis for any chronic respiratory disease diagnosis, except asthma, at any time; and/or
(ii) Received maintenance oral steroids during the baseline year, and/or
(iii) Received multiple FDC ICS/LABA or separate ICS or LABA prescriptions at IPD[b].

Outcome evaluation

Outcomes will be evaluated at **Phase 1,** six months immediately post IPD at which point FP/FOR treatment success will be evaluated.

Outcome measures

In this Phase 1 study, the following will be evaluated

(a) **Change success, defined as:**
Percentage of FP/FOR patients who received ≥2 prescriptions of FP/FOR (i.e. ≥1 prescription in addition to that issued at IPD).

Some patients will change back to their previous FP/SAL MDI because of a resistance to change rather than as a reflection of dissatisfaction with their new therapy. However a

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[b] Multiple prescriptions mean it is not possible to accurately calculate the FDC ICS/LABA dose at point of initiation or change

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change-back rate of >30% is felt to be potentially indicative of dissatisfaction with the change.

(b) **Reason for failure**: where patients receive <1 prescriptions for FP/FOR in the 6-month period post IPD, potential reasons for discontinuation will be evaluated including:

(i) **Occurrence of severe exacerbations** within the 6-month period defined as:
- Asthma-related hospital or emergency room attendance
- Acute oral steroid prescriptions for asthma

(ii) **Loss of asthma control** (in the subset of patients controlled at baseline) where asthma control is defined as absence of the following:
- Severe exacerbations (as defined above)
- GP consultations for lower respiratory tract infections (LRTIs)

(iii) **Adverse events:**[c] the following will be reported for patients who receive <1 prescriptions of FP/FOR post IPD:
- Total number and percentage of patients experiencing each adverse event
- Number and frequency of each adverse event per patient

See **Appendix 1** for further information on how adverse events will be handled and categorised.

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[c] Listed by MedDRA-preferred terms,

Standard Definitions

Asthma-related

The term "asthma-related" includes all events with a **lower respiratory code**, i.e. lower respiratory codes include all those for asthma and LRTIs.

Oral Steroids

(a) Maintenance oral steroids

Where maintenance therapy is defined as daily dosing instructions of ≤10mg prednisolone or prescriptions for 1mg prednisolone tablets.

(b) Acute oral steroids

Acute oral steroid use associated with asthma exacerbation treatment are defined as:

- All courses that are definitely not maintenance therapy, and
- All courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg "as directed"), and
- All courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, and/or
- No or undefined dosing instructions but definitely not maintenance therapy.

Unique exacerbations

Events will be considered to be the result of the same exacerbation (and will only be counted once) where:

- ≥1 oral steroid prescription occurs within 2 weeks of another, or
- ≥1 hospitalisation occurs within 2 weeks of another, or
- ≥1 hospitalisation occurs within 2 weeks of an oral steroid prescription.

Statistical Analysis

The statistical analysis plan will be discussed in full by the Steering Committee before analysis begins. As this is a long-term ongoing study; the analysis for phase 3 is likely to be informed by the results of phase 1.

General

Statistically significant results will be defined as $p<0.05$ and trends as $0.05 \leq p<0.10$.
All analyses will be carried out using SPSS version 19 [13], SAS version 9.3 [14] and Microsoft Office EXCEL 2007.

Summary statistics

Summary statistics will be produced for all baseline and outcome variables, as a complete dataset and by treatment groups. For variables measured on the interval or ratio scale, these will include:

- Sample size (n)
- Percentage non-missing

- Mean
- Variance / Standard Deviation
- Range (Minimum / Maximum)
- Median
- Inter-quartile Range (25th and 75th percentiles)

For categorical variables, the summary statistics will include:
- Sample size (n)
- Range (if applicable)
- Count and Percentage by category (distribution)

<u>Matching and statistical modelling</u>
Matching will be performed to provide a more robust analysis with matching criteria selected as appropriate and informed by cohort characterisation through a combination of categorical and continuous demographic and clinical variables. Any residual differences remaining after matching that are considered to be significant between the treatment arms, or predictive of outcomes, will be considered as potential confounders and will be adjusted for through conditional regression modelling.

Patients will be match on key demographic and disease severity characteristics. The exact matching criteria will be defined following baseline cohort characterisation, but are expected to be:
(i) Age
(ii) Gender
(iii) Short-acting beta agonist use (SABA) – mean daily dose
(iv) Number of oral steroid courses (e.g. 0, 1, ≥2)
(v) Baseline ICS dose (either last prescribed or mean daily as optimises number of matched pairs)
(vi) Number of asthma consultations not resulting in an oral steroid course (e.g. 0, 1, ≥2)
(vii) Date of IPD ± 3 months.

Covariates

Prior research in respiratory disease has identified a range of potential confounders that may affect study outcomes. These include a range of demographic, disease severity, treatment and co-morbid factors. Initial analysis will identify the key baseline confounders, and outcome analyses will take these findings into account and select appropriate statistical methods to minimise potential confounding. These variables will be extracted, where available, for all patients.

Potential confounders examined at (or closest to) the relevant index date:
- Age of patient
- A marker of socio-economic status where possible, i.e. post codes
- Gender of patient
- Height of patient
- Weight of patient
- Body Mass Index (BMI) (in sub-group where BMI can be evaluated)

- Ethnicity
- Lung function, in terms of percent predicted PEF[d] prior to index date
- Smoking status
- ICS or ICS/LABA device type
- ICS drug

Potential confounders examined in the year prior to the index date or ever:

- Date of first asthma diagnosis
- Duration of asthma
- Presence / absence of comorbid rhinitis
- Where rhinitis is present, use of nasal steroids for its treatment.
- Presence / absence of comorbid eczema
- Other important unrelated co-morbidities will be expressed using the Charlson Comorbidity Index (CCI)
- Presence of GERD
- Presence of cardiac disease
- Number of asthma consultations that did not result in a prescription for an oral steroid
- Number of hospital outpatient attendances where asthma is recorded as the reason for referral
- Number of hospitalisations for asthma or possibly respiratory related (a non-specific hospitalisation code and an asthma / respiratory code within a one week window).
- Number of prescriptions for any antibiotic where reason for the prescription is LRTI
- Other medications that might interfere with asthma control:
- Number of paracetamol prescriptions in prior year.
- Number of non-steroidal anti-inflammatory drugs (NSAIDs) prescribed in the prior year
- Number of beta-blocker prescriptions in prior year
- Number of prescriptions for any respiratory therapy (split by number of prescriptions for each) in the prior year
- Number of exacerbations for asthma in year preceding assessment (exacerbation defined above)
- Number of general practice consultations for asthma that did not result in asthma exacerbations treatment and / or other respiratory illnesse antibiotics in prior year.
- Number of hospital outpatient attendances in the prior year where asthma and / or other respiratory illness was the reason for referral.
- Number of hospitalisations for asthma and / or respiratory illness in the prior year (including non-specific hospitalisations with an asthma / respiratory code within a one week window).
- Number of prescriptions for any antibiotic in the prior year where the reason for the prescription is lower-respiratory tract infection.
- Number of short-acting beta-agonist (SABA) prescriptions received in the prior year (calculated based on total combined dose of refilled prescriptions and averaged over 365 days).

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[d] Calculated using Roberts' Equations for adults and Rosenthal's Equations for paediatrics (and incorporating Robinson's Equation for paediatrics ≤1.1m tall).

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- Average ICS daily dose during the prior year (calculated based on total combined dose of refilled prescriptions and averaged over 365 days).
- ICS dose prescribed at index date.
- Spacer use / prescription.
- First or subsequent change (i.e. ≥second change) change of ICS/LABA drug
- First or subsequent step up (i.e. ≥second step-up) from ICS to ICS/LABA dose.

Sample Size and Power Calculations

Prior work by the research team has been used to inform the following power calculations for the 6-month outcome period on this Phase 1 study post launch.

Based on an expected "change-back" probability of approximately 0.20 (20%) among patients changed from existing FP/SAL to FP/FOR at IPD, a sample size of 100 patients would be sufficient to construct a 95% one-sided confidence interval with an upper bound of less than 0.30 (30%) to power the evaluation of FP/FOR "change success".

Limitation of the study design, data sources and analytical methods

As with all real-life database studies, a number of limitations will exist using the real-life OPCRD datasets for which it will not be possible to fully adjust (e.g., potential confounding by severity for factors indiscernible from patient records or patient reported outcomes). While the methods of matching and statistical modelling described in this protocol will address all factors for which it is possible to account, given the internal validity limitations of database studies, the results should be viewed in conjunction with those of other study designs, in particular RCTs.

Dissemination and communication of study results

As with all work undertaken by this research team, the study will be registered with clinicaltrials.gov and the initial results will aim to be presented in poster 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 will aim to be made as soon as the analyses are completed and the results are verified (see the Timelines section of the protocol for anticipated publication dates). Preferred respiratory congresses and journals will be agreed in discussion with Napp Pharmaceuticals, as the study sponsor.

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Researcher Team

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Study Sponsors: Napp Pharmaceuticals
Primary Contact: Rupert Roe

Timetable and Delivery

The estimated timings of the study phases are according to a UK FP/FOR launch date of **September 2012,** with actual first prescription dated Nov 2012.

Total timeframe from project go-ahead to abstract/manuscript development will be 20 months, i.e. based on a September 2012 launch date, the aim will be to complete the Phase 1 manuscript draft by the beginning of June 2014.

Study Phase	Study element	Start date	Completion date
Phase 1 (6-month FP/FOR outcome evaluation)	**Phase 1 study site identification**	Sep 2012	Jul 2013
	Phase 1 data extractions	Aug 2013	Oct 2013
	Phase 1 analysis	Nov 2013	Dec 2013
	Phase 1 report delivery	Jan 2014	
	Phase 1 Steering Committee Meeting	Jan 2014	
	Phase 1 Data Dissemination (Congress Abstract/Poster)	Feb 2014–May 2014	

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APPENDIX 1: Adverse events coding and identification

The OPCRD uses Read codes, hence all Read codes will be converted to MedDRA code and categorised by disease area (e.g. cardiovascular events, renal events) in line with the Read Code categorisations detailed below:

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

Adverse events classification
Data will be extracted on **ALL** adverse events, serious or otherwise.

(a) Adverse events of **particular note** will include the following:[f]

(i)   Local immunosuppressive effects, infections
(ii)   Anaphylactic reactions
(iii)   Psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression
(iv)   Adrenal suppression
(v)   Growth retardation
(vi)   Decrease in bone mineral density
(vii)   Cataract
(viii) Glaucoma

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[f] Items (i)–(xi) have been identified as potential risks of FP/FOR treatment

(ix)　　Hypokalaemia
(x)　　Contusion
(xi)　　Skin atrophy
(xii)　　Hyperglycaemia / increased blood glucose
(xiii)　　Serious asthma-related events (asthma hospitalisations, intubations, deaths)
(xiv)　　Local oral adverse events
(xv)　　Adrenal failure
(xvi)　　Respiratory adverse events including paradoxical bronchospasm
(xvii)　　Cardiac arrhythmias
(xviii)　　Ischemia
(xix)　　All new events – i.e. the event occurs for the first time EVER in the patient's record after initiation of FP/FOR

(b) **Serious adverse events:** In line with the European Medicines Agency ICH Topic E 2 A publication on *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* th[g]e following will be considered to be serious adverse events. Those that (at any dose):

(i)　Result in death
(ii)　Are life threatening[h]

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[g] European Medicines Agency ICH Topic E 2 A publication on *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. June 1995. Available online at:* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf (last accessed 4 August 2011)

[h] "life-threatening" refers to an event in which the patients was a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. The following are considered to have been "life-threatening", an event that: requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.