PASS Protocol	
Drug Substance	MEDI 3250 Q-LAIV Influenza vaccine
Study Code	D2660R00002
Edition Number	1
Date	5 November 2015

A non-interventional study of LAIV utilization to identify and characterize medication errors due to expired vaccine use in individuals 2-17 years of age in the CPRD

EU PAS Register Number:	Study not registered, as yet
Active Substance:	**MEDI 3250 Q-LAIV Flu vax**
Medicinal Product:	Fluenz, Fluenz Tetra
Product Reference:	EU/1/10/661/001, EU/1/10/661/002, EU/1/13/887/001, EU/1/13/887/002, EU/1/13/887/003, EU/1/13/887/004
Procedure Number:	Not applicable
Joint PASS:	No
Research Question and Objectives:	This study is designed to characterize the proportion of patients receiving expired LAIV during two influenza seasons (2013-2014, 2014-2015) based upon data from the CPRD
Countries of Study:	United Kingdom (England and Wales)
Marketing Authorization Holder(s):	MedImmune LLC
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Sponsor:	AstraZeneca

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ASTRAZENECA SIGNATURE(S)

A non-interventional study of LAIV utilization to identify and characterize medication errors due to expired vaccine use in individuals 2-17 years of age in the CPRD

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca

EU QPPV

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PASS information

Title	A non-interventional study of LAIV utilization to identify and characterize medication errors due to expired vaccine use in individuals 2-17 years of age in the CPRD
Protocol version identifier	1
Date of last version of protocol	5 November 2015
EU PAS register number	Study protocol, once finalized, to be registered
Active substance	Influenza vaccine (live attenuated, nasal)
Medicinal product	Fluenz, Fluenz Tetra
Product reference	EU/1/10/661/001, EU/1/10/661/002, EU/1/13/887/001, EU/1/13/887/002, EU/1/13/887/003, EU/1/13/887/004
Procedure number	Not applicable
Marketing authorisation holder(s)	MedImmune LLC
Joint PASS	No
Research question and objectives	This study is intended to provide data to identify and characterize the proportion of expired LAIV administrations during the past two influenza seasons (2013-2014, 2014-15) and to identify risk factors for this medication error.
Country(-ies) of study	United Kingdom
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2. LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this post-authorization safety study (PASS) protocol.

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AZ	AstraZeneca
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GP	General practitioner
ICH	International Conference on Harmonisation
ISAC	Independent Scientific Advisory Committee (for MHRA Database Research)
PASS	Post-authorization safety study
RMP	Risk Management Plan
SAE	Serious adverse event
SAP	Statistical analysis plan
UK	United Kingdom

3. RESPONSIBLE PARTIES

The main responsible parties for this study are listed in Table 1.

Table 1 List of main responsible parties

Role	Name
Medical Affairs Lead(s)	Raja Rajaram, Hervé Caspard
Global Safety Lead	Robert Wise
Global Clinical Lead	Raburn Mallory
Principal Investigator	Robert Brody

Role	Name
Coordinating Investigator (Patient Safety)	Robert Wise
Coordinating Investigator (Medical Affairs)	Hervé Caspard

4. ABSTRACT

Title

A non-interventional study of LAIV utilization to identify and characterize medication errors of expired vaccine administrations in individuals 2-17 years of age in the CPRD

Edition Number 1, 5 November 2015, AstraZeneca (AZ)

Rationale and background

There is a gap in our understanding of the magnitude and character of the number of medication errors consisting of administration of live attenuated influenza vaccine (LAIV) beyond the product expiry date. During the second half of each influenza season the most frequently reported LAIV medication error is typically administration of expired vaccine. Spontaneous reports are not a reliable basis for estimating the incidence rates of use of expired vaccine and may not be representative of all occurrences of this medication error. In addition, the intervals between expiration and vaccine administration may differ from those observed in spontaneous reports.

The intent of the study is to quantify medication errors from expired vaccine administrations, to assess potential factors influencing the proportion of all vaccinations that used expired product, and to describe the intervals between vaccine expiration and vaccination dates. These data could then be utilized as a basis for subsequent assessment of changes over time, e.g., to evaluate the effectiveness of any new measures to increase awareness of LAIV expiration dates.

Research question and objectives

The overall research aim for this study is to identify and characterize the proportion of LAIV administrations that used expired product during the two most recent influenza seasons and to identify risk factors that may be associated with administration of an expired dose of LAIV. In addition, there is interest in quantifying the frequency distribution of days between expiration and vaccination date.

Study design

A cohort of LAIV recipients will be identified from the Clinical Practice Research Datalink (CPRD) database to measure the proportion of expired LAIV administrations to children and adolescents aged 2 through 17 years between September 2013 through March 2014 (influenza

season 2013-2014) and September 2014 through March 2015 (influenza season 2014-2015) as recorded in the CPRD.

Population

The study population is defined as all individuals who received LAIV between September 2013 through March 2014 and September 2014 through March 2015 with a valid LAIV lot identifier recorded in the CPRD and were aged 2 through 17 years at the vaccination date. Based on the vaccine administration date and each valid LAIV lot identifier, the historical cohorts will be classified as having received unexpired vs. expired vaccine.

The expected number of patients who received LAIV during the two time periods is:

Time period	Numbers of subjects aged 2 – 17 years
September 2013 – March 2014	~ 64,000
September 2014 – March 2015	~ 70,000

There is no sampling of the study population to be performed as all available patient records in CPRD will be evaluated.

Subjects with missing or invalid lot identifiers or unknown vaccination dates will be excluded.

Variables

The main event of interest is administration of LAIV after the lot's expiration date. The risk of administration of an expired dose of LAIV will be assessed as a function of other covariates:

- Time of administration: season and timing during the season
- Population characteristics: age, gender, comorbidities, and region
- Characteristics of physician practices, in terms of size and geographic region to the extent that such characteristics are available and permissible

Administration of an expired lot of LAIV will also be characterized as a function of the number of days from lot expiration to LAIV administration.

Data sources

The data sources for this study are the UK Clinical Practice Data Link (CPRD) and AstraZeneca/MedImmune data from manufacturing and/or shipping for valid LAIV lot identifiers and expiration dates.

Study size

The expected number of patients who received LAIV during the two time periods is:

Time period	Numbers of subjects ages 2 – 17 years
September 2013 – March 2014	~ 64,000
September 2014 – March 2015	~ 70,000

There is no sampling of the study population to be performed as all pertinent patient records in CPRD will be evaluated.

Data analysis

Statistical methods for proportions are proposed (Fleiss 2003). Standard errors for proportions for expired vaccine use in the total population of LAIV recipients and as a function of independent variables such as age, gender, comorbidities and time of administration will be calculated for each influenza season and for the pooled pair of seasons. Comparison of the proportions of expired LAIV administrations between the two influenza seasons will be performed by a multivariate logistic (or Poisson) regression after adjustment for potential confounders.

Milestones

Registration in the EU PAS register is planned for 27 November 2015 following ISAC approval. Data collection will begin on 30 November 2015.The final report of study results will be provided by 31 March 2016.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Planned study milestones are listed in Table 2.

Table 2 List of milestones or planned dates

Milestone	Planned date
Protocol signoff	6 November 2015
ISAC submission	13 November 2015
Registration in the EU PAS register	27 November 2015
Start of data collection	30 November 2015

Table 2 List of milestones or planned dates

Milestone	Planned date
End of data collection	4 December 2015
Report of interim study results	30 December 2015
Final Report	31 March 2016

7. RATIONALE AND BACKGROUND

There is a gap in our understanding of the magnitude and character of the number of medication errors comprising live attenuated influenza vaccine (LAIV) administrations beyond the expiry date. During the second half of each influenza season the most frequently reported LAIV medication error is typically administration of expired vaccine. Spontaneous reports are not a reliable basis for estimating the incidence rates of expired vaccine uses and may not be representative of all occurrences of this medication error. In addition, the intervals between expiration and vaccine administrations may differ from those observed in spontaneous reports.

In September 2014, CDC published a short description of a disproportionately high fraction (18.4%) of VAERS reports associated with expired LAIV administrations compared to injectable inactivated influenza vaccine (IIV) (MMWR 2014; 63(35) 773-775). PRAC assessments of PSURs for Fluenz/Fluenz Tetra have also focused on this issue. As a result, a proposal was made to PRAC to systematically study the extent and characteristics of expired vaccine administration. The intent of the study is to provide baseline numbers and characterization of potential factors influencing the proportion of expired vaccine administration and to describe the intervals between vaccine expiration dates and vaccinations. These data could then be utilized as a basis for subsequent assessment of changes over time, e.g., to evaluate the effectiveness of any new measures to increase awareness of LAIV expiration dates.

8. RESEARCH QUESTION AND OBJECTIVES

The overall research aim for this study is to identify and characterize the proportion of expired LAIV administered during the two most recent influenza seasons in the UK.

Primary Objective:

To measure administrations of LAIV beyond the expiry date in individuals aged 2 through 17 years during the past two influenza seasons (September 2013 – March 2014 and September 2014 – March 2015) in the UK through use of the CPRD.

Secondary Objectives:

To investigate risk factors that may be associated with administration of an expired dose of LAIV, including:

- Time of administration: season and timing during the season
- Population characteristics: age, gender, comorbidities, and region
- Characteristics of physician practices in terms of size and geographic region to the extent that such characteristics are available and permissible (by the Independent Scientific Advisory Committee) ISAC for MHRA Database Research

To quantify the frequency distribution of days between dose expiration dates and LAIV administrations.

9. RESEARCH METHODS

9.1 Study design

A cohort of LAIV recipients will be identified from the CPRD database to measure the proportion of expired LAIV administrations to children and adolescents aged 2 through 17 years between September 2013 through March 2014 (influenza season 2013-2014) and September 2014 through March 2015 (influenza season 2014-2015) as recorded in the Clinical Practice Research Datalink (CPRD).

Cohort designs are ideally suited for generating data on attributes of time, patient characteristics, and physician practice characteristics. Confirmation of the medication error use of expired LAIV will require cross reference of the vaccine lot identifier recorded in the CPRD electronic health record with the LAIV lot expiration date located in a separate file provided by AstraZeneca/MedImmune.

9.1.1 Inclusion criteria

The study population for each influenza season will consist of children and adolescents who were administered LAIV from September 1 2013 to March 31 2014 and from September 1 2014 to March 31 2015, aged 2 through 17 years at the time of LAIV administration. All patients with LAIV administration during the influenza season with valid LAIV lot identifiers are included in the study.

9.1.2 Exclusion criteria

Subjects with missing or invalid lot identifiers or with unknown vaccination dates will be excluded.

9.1.3 Sub-populations

There are no pre-specified sub-populations of interest

9.1.4 Follow up

There will be no follow-up required or additional observations of subjects.

9.2 Variables

9.2.1 Events

Administration of expired LAIV will be ascertained by comparison of vaccination dates to expiration dates, drawing the former from CPRD records and the latter from the lot identifier file provided by AstraZeneca/MedImmune.

Administrations of expired LAIV will be counted and characterized as a function of the number of days from lot expiration until LAIV administration.

9.2.2 Covariates

Covariates to be included in the study are those thought to be potential confounders or risk factors for a given outcome of interest. The risk of administration of expired LAIV will be assessed as a function of:

- Time of administration: season and timing during the season
- Population characteristics: age, gender, comorbidities, and region
- Characteristics of physician practices in terms of size and geographic region to the extent that such characteristics are available and permissible, e.g.,
    - Practice size – the number of patients registered to each practice at the index date of the given season
    - Average length of registration at the practice

The covariate list is presented in Table 3.

Table 3 Covariates related to patient, GP practice and time characteristics at time of vaccination

Patient	GP Practice	Time
Gender	Practice size	Season
Age	Average length of registration at the practice	Interval from start of season
Comorbidities	Geographic indicator	
Region	Health Service Area	

9.3 Data sources

The data sources targeted for this protocol include the following:

9.3.1 The Clinical Practice Research DataLink (CPRD): UK

The CPRD is the world's largest computerized database of anonymized longitudinal clinical records from general practice covering approximately 6% of the population in England and Wales, and currently contains over 50 million person-years of data from approximately eight million patients registered with selected general practitioners (GPs). GPs maintain electronic recording for the purpose of patient management during the GP-patient encounters. Since data are collected in a non-interventional way they reflect routine clinical practice in primary care. The GPs agree to provide data to the CPRD for research purposes. The panel of GPs maintained in CPRD is a representative sample of the GP population in England and Wales according to age, sex, and geographical distribution. Additionally, the patient population is representative of the respective country population according to age and sex distribution, as provided by national statistic authorities. The CPRD database is compliant with European and national regulations of patient data protection.

Participating physicians use software to record their daily patient interactions. The electronic data records include demographics (e.g., year of birth, gender, registration dates), medical history (e.g., event dates, diagnosis, symptoms, risk factors, co-morbidities, referrals to consultants and to hospitals), prescription (e.g., prescription dates, therapeutic class, molecule, dosage, posology, duration), and clinical data (e.g., height, weight, blood pressure, immunizations, life habits). Accuracy and completeness of the database have been well documented and validated (Jick, et al., 2003).

9.3.2 Additional data source: LAIV lot identifiers file

Of importance to this study is each lot's expiration date maintained in AstraZeneca/MedImmune files (external to CPRD). Valid CPRD LAIV administrations will have a lot identifier ("lot number") present in the external data file, from which the dose expiration date will be obtained.

9.4 Study size

A total of 64,000 LAIV recipients aged 2 to 17 years were already identified in CPRD during season 2013-2014. Therefore, the proportion of expired administrations can be estimated with a 95% confidence interval width smaller than 0.1%, even if the point estimate is as low as 0.2%. There is no sampling of the population as all LAIV administrations with valid lot identifiers and know vaccination dates will be evaluated. Previous assessment of the number of LAIV administrations within the CPRD database assures that there will be adequate precision in estimation of a range of values for proportions of expired LAIV use.

9.5 Data management

The data source custodian will collect electronic primary care patient records and comply with procedures that include checking electronic files, maintaining security and data confidentiality, following analyses plans, and performing quality checks for all programs.

The database custodian will maintain any patient-identifying information securely on site according to up-to-date standard operating procedures. He or she will also maintain appropriate data storage, and archiving procedures will be followed with periodic back-up of files.

9.6 DATA ANALYSIS

Planned data analyses are summarized within this protocol. Due the straightforward nature of the anticipated analysis, there is no need for a more detailed statistical analysis plan (SAP).

9.6.1 Analysis methods

The receipt of expired LAIV during each influenza season is based on comparison of the LAIV vaccination date in the CPRD record with the corresponding lot expiration date from records maintained by AstraZeneca/MedImmune.

The proportion of individuals receiving expired LAIV vaccine during each influenza season (September 2013 – March 2014 and September 2014 – March 2015) is defined as the number of children and adolescents receiving expired vaccine during each season divided by the total number of children and adolescents with valid lot LAIV administrations during each influenza season.

The proportion of individuals receiving expired vaccine and 95% CIs will be reported. Median intervals and measures of dispersion in days between vaccinations and vaccine expiration dates will also be described.

With due attention to the seasonal time period of receiving an expired LAIV, the proportion of patients receiving expired LAIV as medication errors will be calculated by age group and by gender. Predictors of administration of expired doses will be assessed by a multivariate regression to take into account potential confounders.

The proportion of individuals receiving expired vaccine and 95% CIs will be reported for demographic, physician practice, and time characteristics, and in addition these will be summarized across all regions.

9.6.2 Minimization of bias

The main goal of the study is to estimate the proportion of patients receiving expired LAIV. Covariates include known (as defined by medical or epidemiologic literature) risk factors for the event, confounders between exposure and event, and standard covariates for adjustments, which may include patient, physician, or time characteristics. All covariates will be modeled as continuous or binary indicators.

9.7 Quality control

Standard operating procedures will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans and requirements for senior scientific review.

All work will be subject to quality control and documentation procedures to make certain the final report is accurate and thorough and that the analyses can be reproduced. If the data do not permit an analysis as planned or if clarifying analyses are required, then the missing or the additional information and results will be included in the report(s) and the corresponding explanation made. All key study documents, such as the protocol and study report will undergo quality-control review, senior scientific review, and editorial review.

The data source for this study is considered secondary data from the CPRD. Permission for use of the data will be requested through standard procedures. Analysis will be conducted by contracted personnel with oversight from the investigators who have experience with the database (BB, HC) and are AstraZeneca staff.

A quality-assurance audit of this study may be conducted.

9.8 Limitations of the research methods

The CPRD data represents 6% of the general population of England and Wales. The data recorded is considered to be representative of health resource utilisation by the population. Therefore vaccination data from the CPRD should reasonably reflect the vaccine utilisation throughout the entire country.

This study has a number of limitations that potentially affect the validity of findings or the interpretation of the results. The majority of limitations are inherent to the data sources used in the study and are as follows:

1. Identification of expired vaccine administrations is dependent upon the accurate recording of vaccine lot identifiers within the CPRD data. Despite the efforts taken to define the outcome of interest, the data source to be utilized in this study is a physician-based electronic medical record database; therefore, under-reporting or errors in transcription of vaccine lots into the electronic medical records may occur.

2. Data on vaccination outside the GP practice is extremely limited and at best anecdotal (as there may be text entries indicating that a patient was vaccinated elsewhere). Events occurring in school vaccination clinics will be missed. This study will address only vaccinations during GP encounters as recorded in the CPRD.

9.9 Other aspects

Not applicable.

10. PROTECTION OF HUMAN PATIENTS

The study will be conducted in accordance with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

The study will be registered in the ENCePP Electronic Register of Studies on or before 27 November 2015.

The study will comply with the definition of a non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/European Commission and its refinement provided in Chapter I.7 Section 1 of Volume 9A of the Rules Governing Medicinal Products in the EU: Guidelines on Pharmacovigilance for Medicinal Products for Human Use (European Commission, 2008), and referred to in the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use's Pharmacovigilance Planning (ICH, 2004) and the Guideline on Good Pharmacovigilance Practices, Module VIII—Post-Authorisation Safety Studies (European Medicines Agency, 2012).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Definitions

11.1.1 Definition of adverse events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

11.1.2 Definition of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

11.1.3 Definition of adverse drug reactions

An adverse drug reaction (ADR) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product, suspected to be causally related to the product.

11.2 Collection of adverse events

No active collection of AE data will be performed. However any serious ADR that is inadvertently discovered and has an identifiable patient will be reported, including the study

number, to the PS Data Entry Site. (One or more of the following qualifies a patient as identifiable: sex, age [or category, for example “child”], date of birth, initials, hospital, or other identifying number.) In order to be classified as a serious ADR, the serious criteria must be met, and the medical record should clearly indicate that the treating physician considered there to be a possible causal relationship between the AE and LAIV.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Interim and Final study results will be provided to the European Medicines Agency. An interim study report will be generated by 30 December 2015 and will contain preliminary estimates for the proportion of the population who received expired LAIV and 95% CIs for this outcome of interest. A final study report is planned on or before 31 March 2016 and will be posted on the EnCePP (EMA) PASS Registry.

13. REFERENCES

CDC
CDC REPORTS OF EXPIRED LIVE ATTENUATED INFLUENZA VACCINE BEING ADMINISTERED — UNITED STATES, 2007–2014 **MMWR 2014; 63(35) 773-775**

Fleiss

Fleiss JL, Levin B, Cho Pai M. Statistical Methods for Rates and Proportions. 3rd edition. J Wiley 2003.