Non-Interventional Post-Authorisation Safety Study Protocol

Study ID: NI-PH-X-01

Title of study: Post-authorisation safety study of the incidence rate of medication errors before and after the discontinuation of the lower strength vials for Pharmalgen

Medicinal product:	Pharmalgen (801) *Apis mellifera* Pharmalgen (802) *Vespula* spp.
Active substance:	V01AA07 *Apis mellifera and Vespula* spp. venom
EudraCT No. :	Not applicable
EU PAS register number:	Not registered
Procedure number:	PL10085/0003-0048
Development phase:	IV, non-interventional study
Country:	United Kingdom
Sponsor:	ALK-Abelló A/S
Marketing authorisation holder:	ALK-Abelló A/S Bøge Allé 6-8 2970 Hørsholm
MAH contact person:	Andreas Slyngborg Holst, QPPV
Joint PASS:	No.
Research question and objectives:	To compare the incidence of medication errors and events of serious system allergic reactions with Pharmalgen bee and wasp venom products before and after the discontinuation of the lower strength vials (0.12 µg, 1.2 µg, 12 µg).

Author: Linda Allerslev Nielsen

Document Status: Final

Date: 18-Apr-2017

Version: Version 1.0

QPPV name: Andreas Slyngborg Holst, MD

QPPV signature:

Table of contents

List of tables

List of figures

List of stand-alone documents

None.

List of abbreviations

AE	Adverse event
CH	Switzerland
CIOMS	Council for International Organizations of Medical Sciences
DK	Denmark
DPPV	Distributor Person Responsible For Pharmacovigilance
EDC	Eletronic data capture
GPV	Good pharmacovigilance practice
HLGT	High Level Group Term
ICSR	Individual case safety report
MedDRA	Medical dictionary for regulatory activities
MHRA	The Medicines and Healthcare products Regulatory Agency
NIS	Non-interventional study
NL	The Netherlands
NPPV	National Person Responsible For Pharmacovigilance
OC	Oracle Clinical
PASS	Post-authorisation safety study
PL	Poland
PT	Preferred Term
QPPV	Qualified Person Responsible For Pharmacovigilance
SAE	Serious adverse event
TY	Treatment year
UK	United Kingdom

Protocol synopsis

Title:	Post-authorisation safety study of the incidence rate of medication errors before and after the discontinuation of the lower strength vials for Pharmalgen
Study ID:	Undetermined
Development phase:	Non-interventional study
Rationale and background:	ALK has discontinued production of the lower strengths of Pharmalgen (0.12 µg, 1.2 µg and 12 µg, lower strength vials). Removal of the lower strength vials from the market necessitates a change in the preparation of the up-dosing strengths; instead of using the lower strength vials, all necessary strengths are prepared through manual dilutions of the 120 µg vial. The aim of this PASS is to assess the impact of the removal of the lower strength vials of Pharmalgen on the safety of the patients, when a new dilution scheme for up-dosing is introduced. This study has been prepared by request of the Medicines and Healthcare products Regulatory Agency (MHRA).
Primary objective:	The purpose of this study is to characterize safety of Pharmalgen products after removal of the lower strength vials to evaluate if an increase occurs in medication errors or systemic allergic reactions related to medication errors during the up-dosing phase.
Study design:	Prospective descriptive case study, which aims to compare medication errors and serious systemic allergic reactions related to medication errors reported spontaneously in the United Kingdom (UK) for Pharmalgen products during the defined study period from 01 January 2015 to 31 December 2016 as well as data reported cumulatively.
Study population:	Any patient who initiates immunotherapy treatment with either Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp*.
Study size:	All relevant reports from the UK in the ALK Global Safety Database from 2003 from all spontaneous sources received concerning patients in the up-dosing phase of treatment with Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp*. will be included in this study. In 2015-2016, the overall exposure for Pharmalgen was approximately 1,727 treatment years in the UK, whereof 231 TY concerned initial treatments with the lower strength vials. A similar exposure of initiation treatments is expected in the study period.
Assessments:	The data collected for this study will be spontaneously reported individual case safety reports (ICSRs) of medication errors and serious systemic allergic reactions concerning patients in the up-

	dosing phase of treatment with Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp*. from the UK. A targeted data collection form will be available on all specialist allergy centres. Healthcare Professionals (HCPs) will be trained in filling out the data collection form during their training in the changed dilution procedure. In addition, HCPs will be informed about the data collection form in a Direct Healthcare Professional letter as well as by ALK key account managers visiting the specialist allergy centres. The collected information includes patient data (eg. gender, age, concomitant medication, medical history), treatment phase and detailed information about the relevant events of either medication errors or serious systemic allergic reactions related to medication errors. Follow-up will be requested to ensure that all available information is recorded.
Data sources:	The study will include all relevant reports in the ALK Global Safety Database from all spontaneous sources received concerning patients in the up-dosing phase of treatment with Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp*. from the UK.
Statistical methods:	The number of medication errors and serious systemic allergic reactions related to medication errors will be recorded in the study period and the rate calculated as number of cases divided by number of treatment years. Exact 95% binomial confidence intervals for the calculated rate will be reported.
Product:	Pharmalgen (801) *Apis mellifera* Pharmalgen (802) *Vespula* spp.
Country:	United Kingdom
Study milestones:	Final protocol sent for approval to MHRA — 18 April 2017 Start of data collection — 01 January 2017 End of data collection — 31 December 2018 Final study report — 30 June 2019

Amendments and updates

Not applicable as this is the first version of the study protocol.

1 Introduction

Pharmalgen Hymenoptera Venom products are indicated for diagnosis and treatment of IgE-mediated allergy to Hymenoptera venom and are administered by repeated subcutaneous injections to a person allergic to venom in order to gradually induce immunological tolerance.
The active ingredient in Pharmalgen Hymenoptera Venoms is either Honey Bee (*Apis mellifera*), Yellow Jacket (*Vespula* spp.), Yellow Hornet (*Dolichovespula arenaria*), White Faced Hornet (*Dolichovespula maculata*), Wasp (*Polistes* spp.) or Mixed Vespid (Yellow Jacket, White Faced Hornet & Yellow Hornet), however only Honey Bee (*Apis mellifera*) and Yellow Jacket (*Vespula* spp.) are available in the UK.
These allergen extracts are available in freeze-dried form, and immediately prior to use, the contents of each vial should be reconstituted with human albumin diluent. Treatment with Pharmalgen Hymenoptera Venoms is divided into two phases: an up-dosing/initial phase and a maintenance phase.
ALK has decided to discontinue production of the lower strengths of Pharmalgen (0.12 µg, 1.2 µg and 12 µg, lower strength vials) and only maintain the highest strength (120 µg), as the sale of these lower strengths are very limited. The lower strength vials have been used for preparing the various strengths needed for the up-dosing phase of treatment with Pharmalgen. Removal of the lower strength vials from the market necessitates a change in the preparation of the up-dosing strengths; instead of using the lower strength vials, all necessary strengths are prepared through manual dilutions of the 120 µg vial.

1.1 Background

Pharmalgen is approved in seven countries in the EU, Switzerland, US and Canada. In Germany, the lower strength vials have been available previously, but were withdrawn more than 10 years ago. No medication errors related to preparations of dilutions of Pharmalgen have been received from Germany since the discontinuation of the vials.
The lower strength vials were never marketed in Belgium, France, US and Canada. For Denmark, Netherlands, Poland, Switzerland and United Kingdom, variations to withdraw the lower strength vials have been submitted in 2016. The variations have been approved in Denmark, Netherlands, Poland and Switzerland, and the change to the new dilution procedure for the above mentioned countries took place by 31 December 2016. By 31 March 2017 ALK has not received any reports concerning dilution errors from these countries.

1.2 Rationale

This non-interventional study is designed as a post-authorisation safety study (PASS) by request of the MHRA to assess the impact of the removal of the lower strength vials of Pharmalgen in the UK on the safety of the patients, when a new dilution procedure for up-dosing is introduced.

2 Study objectives

2.1 Primary objective

The objective of this study is to characterize safety of Pharmalgen products after removal of the lower strength vials to evaluate if an increase occurs in medication errors or systemic allergic reactions related to medication errors during the up-dosing phase occurs.

3 Investigational plan

3.1 Overall study design

This study is a prospective descriptive case study, which aims to compare medication errors and serious systemic allergic reactions related to medication errors reported spontaneously in the United Kingdom for Pharmalgen products during 01 January 2017 to 31 December 2018 with data received cumulatively as well as in 01-January 2015 to 31 December 2016.

Specifically, the study aims to:

- Compare received safety data on medication errors related to the up-dosing phase of treatment with Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp* in the UK from 01 January 2017 to 31 December 2018 with data received cumulatively as well as from 01-January 2015 to 31 December 2016
- Compare received safety data on serious systemic allergic reactions related to medication errors in the up-dosing phase of treatment with Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp* in the UK from 01 January 2017 to 31 December 2018 with data received cumulatively as well as from 01-January 2015 to 31 December 2016

The study population includes any patient who initiates allergy immunotherapy treatment with either Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp*.

The data collected for this study will be events of medication errors and serious systemic allergic reactions related to medication errors concerning patients in the up-dosing phase of treatment with Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp*. from the UK spontaneously reported as individual case safety reports (ICSRs).

The information collected from 01 January 2017 includes patient data (eg. gender, age, concomitant medication, medical history), treatment phase and detailed information about the relevant events of either medication errors or serious systemic allergic reactions related to medication errors. Follow-up will be requested to ensure that all relevant available information is recorded. Historical data (cases collected previously to 2017) will be identified in the ALK Global Safety Database.

Cases relevant for this study will be identified by searches in the ALK Global Safety Database for the following MedDRA HLGT and preferred terms (PTs) –

- Medication errors related to up-dosing: HLGT Medication errors
- Serious systemic allergic reactions: PT Hypersensitivity, PT Anaphylactic reaction, PT Type 1 hypersensitivity, PT Anaphylactic shock

All identified cases will be individually evaluated to determine if medication errors related to the removal of the lower strength vials are part of the root cause of the reported events.

All identified cases evaluated to be relevant will be described in detail in the study report.

3.2 Endpoints

3.2.1 Primary endpoint

Cases reported on medication errors and serious systemic allergic reactions related to medication errors in the up-dosing phase of treatment with Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp* in the UK from 01 January 2017 to 31 December 2018, 01 January 2015 to 31 December 2016 and cumulatively until 31 December 2018.

3.3 Study milestones

The planned dates for study milestones are summarised in Table 1.

Table 1 Study milestones

Mile stone	Planned date
Final protocol sent for approval to MHRA	18 April 2017
Start of data collection	01 January 2017
End of data collection	31 December 2018
Final study report	30 June 2019

3.4 Discussion of design

The limitations of this study are related to the low number of reports of medication errors related to up-dosing that are expected to be received for the products, as only few reports have been received cumulatively for medication errors in general. As the study relies on spontaneously reported data, it is a risk that only few or no reports will be received during the time interval, limiting the options for statistical analysis. In order to decrease this risk, a targeted data collection form will be distributed to physicians, who will be trained in completing and submitting the form.

In some cases, limited information may be available with regards to the details of the events that have occurred. Follow-up will be sought to ensure that all relevant available information is included in the relevant cases.

It is not possible to predict what the number of patients initiating treatment with Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp*. will be in 2017-2018. If the number of patients initiating treatment is lower than expected, this could lead to a lower number of relevant reports received.

Educational material describing the dilution procedure for the lower strength vials has been proposed and is to be used for training of specialist allergy centres. In addition a Direct Healthcare Professional letter and a targeted data collection form will be sent to the specialist allergy centres. This should keep physicians focused and aware of the new dilution procedure, and encourage the reporting of any medication errors related to the change in procedure.

3.5 Study population

3.5.1 Selection criteria

The study population includes any patient who initiates immunotherapy treatment with either Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp*.

3.5.2 Patient discontinuation

Not applicable as this relies on spontaneous reporting.

3.6 Treatments

3.6.1 Product

The data collected for this study will be events of medication errors and serious systemic allergic reactions related to medication errors concerning patients in the up-dosing phase of treatment with Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp*. from the UK reported as individual case safety reports.

The sponsor will not pay for any medication or medical care received by the patient during or after inclusion of their data in the study.

3.7 Visit schedule and procedures

Not applicable as this study relies on spontaneous reporting.

3.8 Assessments

The data collected for this study will be events of medication errors and serious systemic allergic reactions related to medication errors concerning patients in the up-dosing phase of treatment with Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp*. from the UK reported as individual case safety reports.

The collected information includes patient data (eg. gender, age, concomitant medication, medical history), treatment phase and detailed information about the relevant events of either medication errors or serious systemic allergic reactions related to medication errors. Follow-up will be requested to ensure that all available information is recorded.

All identified cases will be individually evaluated to determine if medication errors related to the removal of the lower strength vials are part of the root cause of the reported events.

4 Adverse events

4.1 Definitions

4.1.1 Adverse event definitions

An adverse event (AE) is any untoward medical occurrence in a patient or study subject administered a product, which does not necessarily have a causal relationship with this

treatment. An AE can therefore be any unfavourable and unintended sign (including e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product.

This study involves spontaneous reports received by ALK from all available sources. Analysis of the received reports will occur after the cases have been processed and added to the ALK Global Safety Database.

The focus of this study is medication errors and serious systemic allergic reactions related to medication errors. A medication error is defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. A medication error may occur without any associated adverse event. In this study, medication errors will be identified by using the term HLGT Medication errors. Serious systemic allergic reactions are any systemic allergic reaction assessed to be serious according to the criteria in section 4.1.2. Serious systemic reactions will be identified in the ALK global safety database using the MedDRA search terms PT Hypersensitivity, PT Anaphylactic reaction, PT Type 1 hypersensitivity, PT Anaphylactic shock.

4.1.2 Serious adverse event definitions

A serious adverse event (SAE) is any untoward medical occurrence or effect that:

- Results in death
- Is life-threatening[a]
- Requires in-patient hospitalisation[b]
- Results in persistent or significant disability or incapacity[c]
- Is a congenital anomaly or birth defect
- Is judged medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed).

a) This refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe
b) The term hospitalisation is used when a subject:
    - Is admitted to a hospital or in-patient, irrespective of the duration of the physical stay or
    - Stays at the hospital for treatment or observation overnight
c) A substantial disruption of a subjects ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity or quality of life

A non-serious AE is any AE that does not meet the definition of an SAE.

4.2 Collection, recording and reporting of adverse events

This study involves spontaneous reports which will be received, processed and submitted according to the established procedures in ALK Global Pharmacovigilance. Analysis of the received reports will occur after the cases have been processed and added to the ALK Global Safety Database.

5 Data management

5.1 Data collection

The study will include all reports of medication errors and AEs associated with medication errors in the ALK Global Safety Database received since 01 January 2003 from all spontaneous sources received concerning patients in the up-dosing phase of treatment with Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp*. As sales data for Pharmalgen is available from 2003 and onwards, the data cut-off for this study will be 01 January 2003.

A targeted data collection form will be available on all specialist allergy centres. Healthcare Professionals (HCPs) will be trained in filling out the data collection form during their training in the changed dilution procedure. In addition, HCPs will be informed about the data collection form in a Direct Healthcare Professional letter as well as by visiting ALKs key account managers.

5.2 Data processing

All case reports included in this study will be processed according to established case handling procedures in ALK Global Pharmacovigilance (see section 6). Relevant cases will be identified using the PTs defined in section 3.1.
Individual case safety reports (ICSRs) are received locally at the affiliates, distributors or partners level and forwarded to and processed by GPV.
The National Person Responsible for Pharmacovigilance (NPPV), Distributor Person Responsible for Pharmacovigilance (DPPV) or partner ensures that all necessary information has been collected, translated and forwarded to GPV. An ICSR form and a copy of all source documentation including ICRS forms is forwarded to GPV for case processing.
When the report reaches GPV, Safety Operations perform triage, book-in, data entry and 1st review (verification). Thereafter the case moves into scientific/medical evaluation (2nd review) performed by the Safety Surveillance team. Submission of expedited reports to competent authorities (CAs) and distribution to partners and affiliates is performed by Safety Operations. Follow-up requests and closing of cases is also performed by the Safety Operations team. After 2nd review is complete the ICSRs applicable for CA via E2B are submitted. Safety Operations ensures the global distribution of CIOMS to the affiliates or partners for the cases that needs local submission in paper version. All information received by ALK is managed with due considerations to current data protection regulation, as applicable.
Upon evaluation follow-up information is requested. Partners are notified and involved as specified in Pharmacovigilance agreements. AE reports from headquarter-initiated clinical trials are entered into the clinical database Oracle clinical (OC) or stored in the Electronic data capture (EDC) system, while local clinical trials conducted by affiliates are entered into a local database. A case report form standard for reporting of adverse events is followed. When needed overviews of AEs across trials (OC, EDC and affiliates) may be produced.

6 Quality control

The data quality and integrity of the included cases are ensured by the established case handling procedures in GPV (see section 5.2).

Specific follow-up will be requested to ensure that the included reports concern events related to the up-dosing phase.

6.1.1 Recording of data and retention of documents

A complete file for each individual case safety report is available in the Global Safety Database. Source data from before 01 January 2015 are stored in fire safe protected location in ALK Headquarter. From 01 January 2015 all cases are stored electronically including all available source documentation, copies of such, communication and forms related to case handling. Only GPV employees are allowed to retrieve files from the locked fire safe.

7 Statistical methods

The number of medication errors and serious allergic reactions related to medication errors will be recorded in 2017-2018 and the rate calculated as number of cases divided by number of treatment years. Exact 95% binomial confidence intervals for the calculated rate will be reported.

7.1 Sample size and power considerations

In 2015-2016, the overall exposure for Pharmalgen (801) *Apis mellifera* or Pharmalgen (802) *Vespula spp* was approximately 1,727 treatment years in the UK, whereof 231 TY concerned initial treatments with the lower strength vials. A similar exposure of initiation treatments is expected in the study period.

7.1.1 Sample size considerations

No formal sample size calculation is made for this study and no hypothesis testing is done. This section illustrate the precision obtained in different scenarios based on historical data.

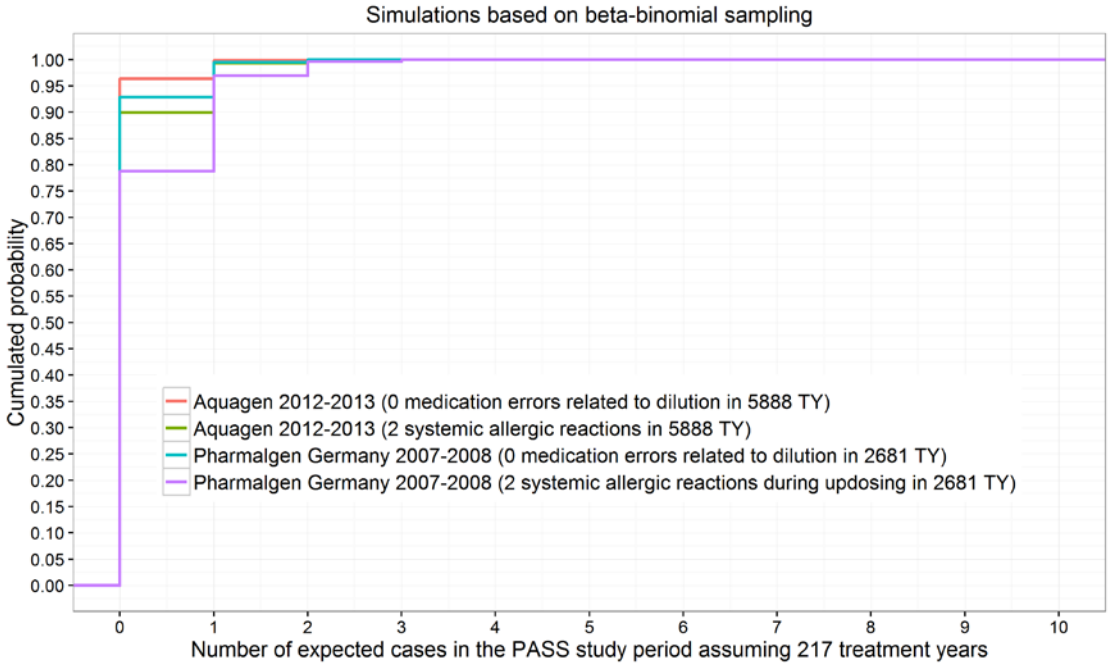
Table 2 shows historical data for the number of HLGT Medication errors and serious systemic allergic reaction reported during the up-dosing phase in two similar situations; vial 1-3 was removed for Pharmalgen in Germany 01 January 2007 and vial 1-3 was removed for Aquagen in Germany, Finland, Denmark and Sweden 01 January 2012.

Table 2 Safety surveillance data for Pharmalgen and Aquagen: HLGT Medication errors and serious systemic allergic reactions during the up-dosing phase.

				AEs during up-dosing phase			
Product	(Countries)	Time period	Treatment years (TY)	HLGT Medication errors	HLGT Medication errors related to the preparation step (dilution)	Overall number of cases of serious systemic allergic reactions reported during up-dosing phase	Number of cases of serious systemic allergic reactions related to the preparation step (dilution)
Pharmalgen	(Germany)	01Jan2007-31Dec2008	2681	0	0	2	0
Aquagen	(Germany, Finland, Denmark and Sweden)	01Jan2012-31Dec2013	5888	1	0	2	0

Based on the data in Table 2 the number of medication errors related to dilution and serious systemic allergic reactions in the up-dosing phase can be simulated by beta-binomial sampling under the assumptions that the underlying probability for medication errors and serious systemic allergic reactions for Pharmalgen in the PASS study period is the same as for the historical data. Furthermore, it is assumed that the number of treatment years is 217 (2 times treatment years in 2016) in the PASS study period. Figure 1 shows the cumulated distribution of the simulated number of cases.

Figure 1 Simulated number of medication errors and systemic allergic reactions during updosing



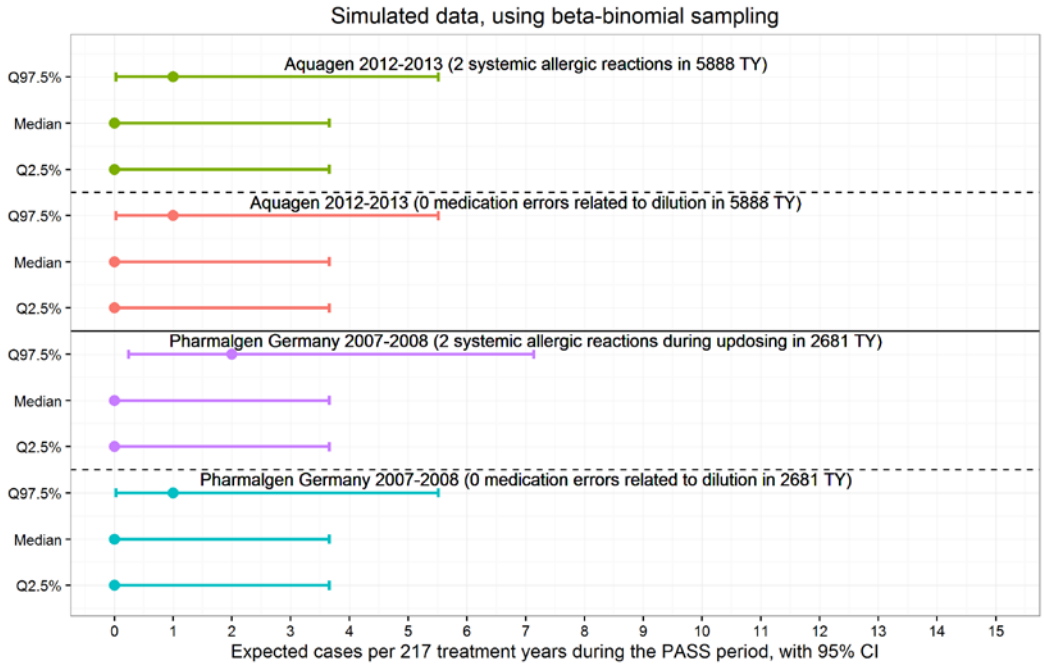
For all four scenarios illustrated in Figure 1, the median of the expected number of cases is 0 for the assumed 217 treatment years in the PASS study period. To further illustrate the results and precision for the simulated outcomes exact 95% binomial confidence intervals is calculated for different quantiles in the cumulated distribution shown in Figure 1. The number of cases and the corresponding 95% confidence limits are shown in Table 3 and illustrated in Figure 2.

Table 3 Exact 95% binomial confidence intervals for selected quantiles in the simulated data (based on 217 TY).

Data source	Quantile	Predicted	Lower 95% CI	Upper 95% CI
Pharmalgen: Germany 2007-2008 (0 medication errors related to dilution in 2681 TY)	Q2.5%	0	0	3.66
	Median	0	0	3.66
	Q97.5%	1	0.025	5.51
Pharmalgen: Germany 2007-2008 (2 systemic allergic reactions during up-dosing in 2681 TY)	Q2.5%	0	0	3.66
	Median	0	0	3.66
	Q97.5%	2	0.243	7.14
Aquagen: Germany, Finland, Denmark and Sweden 2012-2013 (0 medication errors related to dilution in 5888 TY)	Q2.5%	0	0	3.66
	Median	0	0	3.66
	Q97.5%	1	0.025	5.51
Aquagen: Germany, Finland, Denmark and Sweden 2012-2013 (2 serious systemic allergic reactions during up-dosing in 5888 TY)	Q2.5%	0	0	3.66
	Median	0	0	3.66
	Q97.5%	1	0.025	5.51

The expected outcomes and 95% confidence intervals are further visualised in Figure 2

Figure 2 Exact binomial confidence intervals for the 5% quantile, median and 95% quantile for medication errors and serious systemic allergic reactions during the up-dosing phase.



In conclusion, 0 medication errors related to dilution and 0 serious systemic allergic reactions during up-dosing are expected during the PASS study period.

7.2 Definition of analysis sets

Cases relevant for this study will be identified by searches in the ALK Global Safety Database for the following –

- Medication errors related to up-dosing: HLGT Medication errors
- Serious systemic allergic reactions: PT Hypersensitivity, PT Anaphylactic reaction, PT Type 1 hypersensitivity, PT Anaphylactic shock

All identified cases will be individually evaluated to determine if medication errors related to the removal of the lower strength vials are part of the root cause of the reported events.

8 Protection of human subjects

All information contained in the received cases included in this study will be handled in a manner ensuring confidentiality and protection of patient personal data.

As this study is performed using case reports received from spontaneous sources, the planned analysis is consistent with routine pharmacovigilance surveillance activities performed for the concerned products. Patient consent or withdrawal, as well as Ethical Committee approval is therefore not relevant for this study.

9 Reporting of results

9.1 Study report

The study report will accurately and completely summarise the study objectives, methods, results, and interpretation of the findings.

The study responsible will review and sign the study report.

9.2 Publication of results

A final report will be prepared and submitted to the MHRA on 30 June 2019.

10 Reference list

Not applicable as no references has been included in the document.

11 Annexes

11.1 Annex 1

No stand-alone documents have been included in the document.

11.2 Annex 2

ENCePP checklist for study protocols.

Study title:

Post-authorisation safety study of the incidence rate of medication errors before and after the discontinuation of lower strength vials for Pharmalgen

Study reference number:

NI-PH-X-01

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection	☒	☐	☐	3.3
1.1.2 End of data collection	☒	☐	☐	3.3
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	3.3

Comments:
1.1.5: The study will be registered in the EU PAS register after MHRA has approved the study protocol.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	Front page
2.1.2 The objective(s) of the study?	☒	☐	☐	2.1
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	3.5.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	3.1

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	3.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	5.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	7
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	5.1

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	3.5.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	3.1
4.2.2 Age and sex?	☐	☒	☐	
4.2.3 Country of origin?	☒	☐	☐	3.1
4.2.4 Disease/indication?	☒	☐	☐	3.1
4.2.5 Duration of follow-up?	☐	☒	☐	3.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	3.5.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	3.5.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	7.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

5.1 & 5.3 All patients who initiate immunotherapy with Pharmalgen are included in the study.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	3.2.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7 & 7.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☒	☐	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	3.4
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	☒	
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	3.1
9.1.3 Covariates?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	3.1
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	3.1
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	4.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	4.2
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

9.3: It is referred to ALKs internal procedure in where dictionaries as e.g. MedDRA are described.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☐	☒	☐	
10.2 Are descriptive analyses included?	☒	☐	☐	7
10.3 Are stratified analyses included?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	7.1

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	6.1.1
11.2 Are methods of quality assurance described?	☒	☐	☐	6
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☐	☐	☒	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	

Section 13: Ethical issues	Yes	No	N/A	Section Number
13.3 Have data protection requirements been described?	☐	☐	☒	

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☐	☐	☒	

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	9.2
15.2 Are plans described for disseminating study results externally, including publication?	☐	☒	☐	

Comments:

Name of the main author of the protocol: Linda Allerslev Nielsen

Date: 18 April 2017

Signature: _____