PASS protocol preliminary assessment report

A Multicentre, Non-interventional, Prospective, Observational Drug Utilisation Study of Ayendi Nasal Spray Prescribed as Treatment in Emergency Departments in the United Kingdom (UK)

Ayendi 720microgram/actuation Nasal Spray

Ayendi 1600microgram/actuation Nasal Spray

(Diamorphine)

Market Authorisation Holder: Wockhardt UK Ltd

Date: 05/05/2016

Update: 04/08/2016

Administrative information

Title	**A Multicentre, Non-interventional, Prospective, Observational Drug Utilisation Study of Ayendi Nasal Spray Prescribed as Treatment in Emergency Departments in the United Kingdom (UK)**
Protocol version identifier	**Draft 0.8.1 Dated 05/11/2015**
Date of last version of protocol	5/11/2015
EU PAS register number	*N/A*
Active substance	**Diamorphine (as Hydrochloride)** **ATC Code: N02AA09; Natural opium alkaloids**
Medicinal product	**Ayendi 720microgram/actuation Nasal Spray** **Ayendi 1600microgram/actuation Nasal Spray** **Ayendi will be supplied by hospital pharmacy (not by Sponsor) as part of routine ED practice.**
Product reference	**PL29831/0465 (720µg/ actuation); PL 29831/0466 (1600µg/ actuation);**
Marketing authorisation holder	**Wockhardt UK Limited, Ash Road North, Wrexham Industrial Estate, Wrexham, LL13 9UF**
Joint PASS	No
MAH contact	**Gordon Urquhart, Wockhardt UK Limited** UK
Research question and objectives	**The purpose of this prospective observational study is to evaluate the practical usage of the product as a treatment post authorisation.**
Country of study	United Kingdom
Author	**Therakind Limited, Third Floor, 314 Regents Park Road, London N3 2JX**

Name of the contact and assessor	**Name:** Dr Nicola Parkinson ☎ +44-020-3-080-6811 **Email:** Nicola.Parkinson@mhra.gsi.gov.uk

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List of abbreviations

%CV	Coefficient of Variation calculated using $100 \times \sqrt{e^{s^2} - 1}$, where s^2 is the variance of the log transformed data
AE	Adverse event
ATC	Anatomic Therapeutic Code
CRF	Case report form
ED	Emergency Department
GCP	Good clinical practice
IEC	Independent ethics committee
Kg	Kilogram
MA	marketing authorization
Mg	Milligram
µg	Microgram
MHRA	Medicines & Healthcare products Regulatory Agency
Ml	Millilitre
µl	Microliter
PASS	Post Authorisation Safety Study
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event
WHO	World Health Organisation

1. Background information on the procedure

1.1. About the procedure

As a condition of the MA authorisation, the MHRA requested Wockhardt UK Limited to undertake a PASS to evaluate use in emergency departments (where intended to be used) within the UK.

The 12 month observational study will be undertaken with the following milestones:

Milestone	**Planned date**
Start of data collection	Estimated at Q3 2015
End of data collection	Estimated at 12 months post start of data collection
Interim study progress report	Estimated at 6 months post start of data collection
Final report of study results	12 months post end of data collection

Assessor's Comments
The milestones are acceptable for this short term 12 month study.

2. Rationale and background

Wockhardt UK Limited, in collaboration with Therakind Limited, has developed a new dosage form, specifically for nasal use, of the off-patent product diamorphine hydrochloride for use in children as an analgesic for the relief of acute pain – diamorphine hydrochloride nasal spray (Ayendi Nasal Spray). The device delivers the drug as a very fine mist into the richly vascularised nasal epithelium.

Two studies have been completed in order to support the clinical development of this product, a pharmacokinetic study (DIA001)[1] and a safety study (DIA002)[2].

On review of the marketing authorisation application by MHRA, it was noted that the safety study (DIA002) highlighted difficulties of administering the product in the Emergency Department (ED). This post-authorisation safety study (PASS) (DIA003) was requested by MHRA to evaluate the practical usage of the product as a treatment in the Emergency Department. The study will assess the patterns of use particularly in relation to aspects that may have an impact on the safety of the product (e.g. co-medication [including other opioids], medication errors). The study will also assess the effectiveness of routine risk minimisation activities. **The study is observational with no intervention – data not recorded as routine clinical practice should not be recorded on the CRF.**

Ayendi Nasal Spray is available commercially in two strengths:

- Ayendi 720microgram/actuation Nasal Spray
- Ayendi 1600microgram/actuation Nasal Spray

The product is comprised of diamorphine hydrochloride, freeze dried powder reconstituted with 0.5% preserved saline solution and administered in a nasal spray device, equivalent to 720µg OR 1600µg in each spray.

This will be prescribed and administered in the ED of sites included in the observational study, theoretically in accordance with the approved SmPC.

The study will be conducted in compliance with the protocol, ICH GCP and the applicable regulatory requirement(s).

3. Research question and objectives

The Primary objectives of this study are to:

To determine the rates of:

- Doses given (mg/kg) which deviate from the posology as written in the SmPC. Previous opioid usage immediately prior to Ayendi (%)

Secondary objectives

- Time of administration (including pre-arrival at hospital, if appropriate)
- Dose Prescribed (mg/kg) vs. Dose Given (mg/kg)
- Product strength and Number of sprays given
- Diagnosis for which Ayendi was prescribed (% used for off- label indications)
- Participating ED practice setting (%)
- Administrator (%)
- Concomitant medication
- Patient demographics (including patients who do not fit within the categories defined in the SmPC).
- Adverse events (%)

4. Research methods

4.1. Study design

This is purely an observational study. The attending physician will provide routine standard of care and prescribe medicinal products as per hospital standard of care and the patient's requirements.

In order to provide the potential of obtaining the broadest cohort, consent will be taken **after** the patient has been given the Ayendi Nasal Spray as part of routine clinical practice.

After Ayendi has been administered but before the patient is discharged from the ED, the hospital staff will approach the adult patient/parent(s)/legal guardian/patient (whichever is applicable) to discuss the use of the patient's data for research purposes. If the adult patient/parent(s)/legal guardian(s)/patient (whichever is applicable) agrees to the inclusion of the patient's data in the study, the hospital staff will transcribe the required data from the ED records onto study specific Case Report Forms. Data not recorded as routine practice on the ED records and patient notes should not be recorded on the CRF, even if the information is available.

The **study period** is defined as the time after the patient was administered Ayendi until they are discharged from the ED. After the patient has been treated in the ED, they may be discharged or

transferred to a hospital ward. There will be no follow-up information recorded once the patient has been discharged from the ED.

4.2. Setting

Summary

A minimum of 20 sites across the UK will be included; they will be selected to ensure stratification for teaching and non-teaching hospitals, geographical coverage, department size, experience with diamorphine, and combined or separate paediatric EDs.

Selection of subjects

The MHRA have requested that no age range is defined in order to capture all data on Ayendi use. Hence data from patients dosed outside the SmPC restrictions will be collected, to provide a comprehensive review of use in clinical practice. Thus any patient who has been prescribed Ayendi as part of routine treatment in the ED is eligible for the study.

Inclusion criteria

To be eligible for inclusion into this study the subjects must fulfil all of the following criteria:

1. Patient has been administered Ayendi Nasal Spray by the attending ED Healthcare Professional as part of ED treatment.
2. Parent(s)/legal guardian/adult patient (whichever is applicable) must be able and willing to provide written informed consent before the patient is discharged from the ED.
3. Where possible, child patients should assent to allow their data to be used for the study.

Exclusion criteria

None

Withdrawal criteria

Parent(s)/legal guardian(s)/ adult patients (whichever is applicable) may withdraw consent for their data to be included in the study at any time without their care being affected.

No data will be recorded on a CRF for a patient if consent for its use has been withdrawn.

4.3. Variables and data sources

All clinical data to be collected for the study will be transcribed from the ED records onto study specific CRFs by the ED staff.

Clinical data which are not recorded routinely in the ED records as part of clinical practice should not be included in the CRF, even if the information is available.

Information transcribed directly from the ED records (where available):

- Demographic data: weight, age, gender
- Indication (site and nature of injury/trauma) / diagnosis
- Relevant current and ongoing medical history
- Concomitant medications taken during the study period
- Details (name, position, qualifications) of the Ayendi administrator
- Time of dose

- Strength and dose of Ayendi prescribed
- Strength and dose administered
- Any issues with dosing
- Adverse events that occur prior to discharge/transfer from the ED
- Serious Adverse Events that occur prior to discharge/transfer from the ED

Study-specific information from the informed consent form and the study identification log includes the following:

- Unique subject identifier to identify site and subject number in study
- Administration setting
- Date of informed consent (subject assent, if applicable)
- Confirmation of adherence to inclusion criteria

In addition to individual Case Record Forms, the following information will be collected by the Clinical Research Associate at each site as part of the site initiation and routine monitoring visits:

- How Ayendi is generally prescribed
- How Ayendi is routinely administered
- How Ayendi administration is recorded in the controlled drug logs
- Steps taken by the site to minimise dosing error

This is purely an observational study and no further information will be documented as part of the study.

Assessor's comments

Given that this study is to be based in a setting where there is experience in the use of intra-nasal administration of diamorphine; information should be obtained as to whether training has been undertaken in the use of Ayendi prior to study start, or whether it has been considered unnecessary.

4.4. Study size

Summary

The study will aim to recruit a minimum of 400 patients who attend the hospital emergency department and are administered Ayendi Nasal Spray.

The sample size has been powered to accurately estimate both the rate of incorrect dosing and use in association with other opioids.

The rate of incorrect dosing and concomitant opioid use are based on the previous DIASAFE study (DIA002). In that study 14 of 226 subjects (6%) received the incorrect dose and 5 of 226 subjects (2%) received concomitant opioids defined as any other opioids (including any given if Ayendi/diamorphine is insufficient treatment) received from the time of the injury until the subject's discharge from the ED.

Regardless of event rate, 400 subjects will provide a maximum half-width of the 95% confidence interval (based on a normal approximation) of 4.9%. With this sample size, the half-width of the 95% confidence interval for the incorrect dosage rate is 2.3% and for the opioid usage rate is 1.4%. Thus a sample size of 400 subjects provides precise estimates for a range of rates.

4.5. Data management

Data will be collected on paper-based CRFs at site by the site staff. No data will be directly captured on to the CRF.

The database design will be set-up by Syne Qua Non within a fully validated clinical database data management system, Syne-clin II, in accordance with Syne Qua Non's standard operating procedures. All data will be entered onto Syne Qua Non Ltd computer database by a member of the data management section and then verified by repeat data entry by a further section member. Standard Query Language edit checks (as defined in the Study Validation Plan) will be used to validate the data post entry. The consistency reviews will be performed by exporting the data into Excel and manipulating it with a series of filters.

Assessor's comments
Information should be submitted on the validation of the data management system to be used, i.e. if according to nationally authorised/utilised standards.

4.6. Data analysis

A statistical analysis plan (SAP) will be developed by a qualified statistician and analysis will be performed according to this document. The SAP will specifically include details of how all: Analysis Populations, Demographic and Baseline Characteristics, Completion and Discontinuation information, Medication details and All Analyses (rate of incorrect dosing, rate of previous opioid usage immediately prior to Ayendi, time of dosing, product strength and number of sprays, indication, ED practice setting, administrator, concomitant medication, and adverse events) will be classified and described. The SAP will be reviewed and approved prior to database lock.

The sample size chosen for the study is considered appropriate based on previous experience. This is an observational study of patients receiving prescribed Ayendi in a UK Hospital Emergency Department. The sample size will have sufficient power to estimate both the rate of incorrect dosing and use in association with other opioids.

Changes in the conduct of the study or planned analyses will be reported in the corresponding section of the study report.

Analyses

Reporting of the data will be of a descriptive nature and presented using appropriate summary statistics (e.g. n, mean, SD, %CV, median, minimum, maximum) or frequency distributions (n%) by age group (e.g. age 2-11 years, age 12-<16 years, and otherwise, as appropriate) and weight bands (based on those described in the SmPC, and otherwise, as appropriate). Unless otherwise stated these tabulations will be supported by data listings.

Assessor's comments: stratifications should be undertaken at the end of the study on the complete dataset. Stratifications should be based on the SmPC patient groups in terms of age and weight, as specified in the combined SmPC posology's as well as those patients who are outside the authorised age groups. If there is a general lack of data available to support this stratification, then a suitable stratification should be proposed to be applied equally for ages and weights.

Summaries will include all patients for whom appropriate informed consent was obtained to allow collection of their data. AEs will be coded according to the current version of MedDRA (version to be identified in study report).

Concomitant medications will be listed and coded according to Medication class (WHO ATC Level 2) Standardised medication name (WHO ATC Level 4).

Treatment emergent adverse events (TEAEs) will be determined and only these will be included in the statistical analysis report. Details of the criteria of classifying an AE as a TEAE will be provided in the Statistical Analysis Plan (SAP).

The incidence of adverse events will be summarised by system organ class, preferred term and maximum severity. Adverse events will also be summarised by strongest relationship to Medicinal Product by event and system organ class. If a patient experiences an adverse event more than once, the event with the worst severity or at the most related to MP occurrence will be considered. Patients will be included only once at each level where they experienced one or more events.

A summary of the incidence of serious adverse events will be presented by event and system organ class.

Data Analysis

Statistical analyses will be performed after all patient data have been collected, protocol deviations reviewed, populations have been agreed and the database has been locked.

Details of all analyses will be included in the SAP.

Continuous variables will be summarised using descriptive statistics; n, mean, standard deviation, median, minimum and maximum, while categorical variables will be summarised as the number (and percentage) of patients in each category.

Demographic data will be summarised overall and by weight in accordance with the approved posology categories, and otherwise, as appropriate.

Concomitant medications will be tabulated by weight group along with the current available WHO drug dictionary coding by primary term and generic drug name.

Safety analyses will be simply summarised.

Adverse events will be coded according to the current version of MedDRA.

Missing, Unused or Spurious Data

The handling of missing, unused and spurious data will be described in the SAP.

Deviations from the Planned Statistical Analyses

Any changes to the planned analysis (as described in the protocol and SAP) will be documented in the statistical and clinical study reports.

4.7. Quality control

An appropriate number of sites will be selected for audit by an independent auditor.

In order to check the compliance of the study regarding GCP, audits may be carried out by a quality assurance representative. The investigator will provide access to authorised persons during regulatory authority inspections or Sponsor audits.

Study Monitoring

Appropriately qualified and trained staff will be involved in this study. Staff at the investigational site will be instructed in the conduct of the study according to this protocol.

Sponsor personnel will monitor the site on a 4 to 8 weekly basis during the study recruitment phases to assure adherence to the protocol. During these visits, the CRFs and other study documentation will

be checked for accuracy and completeness, and to permit 100% source data verification for 10% of transcribed records.

The investigator will agree to provide the monitor direct access to the patients' source data, which may exist in the form of hospital records, patient files and notes, and laboratory assessment reports and results.

Trial Documentation and Storage

The investigator/institution should maintain the trial documents in a comprehensive and centralised filing system that is suitable for inspection by representatives of the Sponsor and regulatory authorities. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents as defined by ICH GCP include the signed protocol and any amendment(s), copies of the completed CRFs, signed informed consent forms from the parent(s)/legal guardians of all patients for whom consent was obtained, hospital records and other source documents, REC approvals and all related correspondence including approved documents, site delegation lists and curriculum vitae, study correspondence and a list of the patients' names and addresses.

The principal investigator must retain copies of all essential documents for the period specified by ICH GCP and by applicable regulatory requirements.

The principal investigator will inform the Sponsor of the storage location of the essential documents and must contact the Sponsor for approval before disposing of any of these documents.

It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The Sponsor should be informed immediately by the investigator/institution of any change concerning archiving facilities.

Handling, processing, storage and destruction of data will be compliant with the Data Protection Act of 1998.

4.8. Limitations of the research methods

- As this is an observation study of post authorisation drug utilisation, the sites included in this study are limited to EDs which have independently, without reference to this study, made the decision to use Ayendi.
- In an effort to avoid bias, sites will be included that have a history of the use of nasal diamorphine as well as sites that have rarely or never administered it prior to purchasing Ayendi. Additionally, units that have a dedicated paediatric ED department as well as those that are part of the general adult ED will be included. Also, recruitment per site will be limited to a maximum of 60 patients (15% of the overall sample size) to ensure that the overall estimate is not too affected by one site. By use of these measures, and having a patient population of 400, bias will be reduced, and a representative position of the UK EDs should be obtained.

Consideration of potential bias introduced by the consent processes

- It is well documented that consenters and non-consenters (including proxy consent) can differ, that getting consent can be challenging, but that full consent is generally expected in many areas of research. An observational study design where consent is not taken until after the patient receives Ayendi as part of routine clinical practice somewhat reduces the bias introduced by the consent process, thus capturing the true patient population. However, consent may be more or less likely depending on whether other opioids are given, or if incorrect dosing is used. In particular, if incorrect dosing has clinical consequences patients/parents/legal guardians may be less likely to consent and results could be biased downwards.

Therefore, the MHRA have requested a separate data extraction be conducted where investigators and their teams will extract, then anonymise, retrospective data from patient case notes without actively seeking consent.

The summary data from this retrospective data extraction will be used to provide validation for the results of the prospective study.

In order to collect a similar level of detail in the information from the two studies so as to ensure reasonable comparability between the data sets of a prospective and a retrospective study, no clinical data outside of what is routinely recorded in the ED records will be collected for the prospective study, DIA003.

A minimum of 5 sites will provide the retrospective, anonymised data on a number of additional patients who have been dosed with the product. Timing and number of patients will be agreed in advance on a site by site basis.

It is anticipated that sites in the retrospective data extraction will not have participated in the prospective study. However, due to the practicalities of obtaining retrospective data on a new medicine, sites from the prospective study may need to be included. The busy nature of an emergency department means there will have been patients at these sites who were treated with Ayendi but who were not approached to provide consent to participate in the prospective study.

However, if patients were approached for the prospective study and refused consent, their case notes will not be included in the retrospective data extraction.

The retrospective data extraction will likely begin towards the end of the prospective study due to the practicalities of obtaining retrospective data on a new medicine. Approval for this retrospective data extraction will be sought separately.

End of study

For administrative and safety reporting purposes the end of the study will be defined as after the last patient's hospital discharge. This provides for a single and conservative definition

5. Protection of human subjects

The study will be planned, initiated, managed and reported with safeguards in place in order to comply with national and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies. That is:

- The study will be initiated, managed and financed by Wockhardt voluntarily or pursuant to obligations imposed [by regulators] and which involve the collection of data on suspected adverse reactions from patients or healthcare professionals
- Payments to healthcare professionals for participating in study shall be restricted to the compensation for time and expenses incurred
- The MHRA may require Wockhardt to submit the protocol and the progress reports
- The protocol will be actively approved by the MHRA prior to study commencement
- Substantial Protocol amendments will be actively approved by the MHRA
- Wockhardt will send the final report to the MHRA within 12 months of the end of data collection
- Automatic, formal assessment and decision-making will be based on the results of the study
- Any new information which might influence the evaluation of the risk- benefit balance of the medicinal product shall be communicated from Wockhardt to the MHRA
- Wockhardt will update the product information, as appropriate following this process

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and are consistent with ICH-GCP (effective as of 17-JAN-1997) and applicable regulatory requirements. Regulatory authorities will be notified and consulted as required prior to, during, and after the conduct of the study.

Informed consent

Before the data of a patient under the age of 18 years old can be included in the study, their parent(s)/legal guardian must give written informed consent to the data inclusion. Where applicable, the patient themselves will provide assent for the study (generally in patients over 7 years of age). Adult patients capable of consent must provide written informed consent to the inclusion of their data.

Patient information leaflets about this study will be provided which target specific age groups and levels of understanding in order to obtain patient assent for the study as well as for adult patient/parental/legal guardian consent.

Patient Confidentiality

The principal investigator must ensure that the patient's anonymity is maintained. On the CRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by their assigned identification number and initials only. If patient names are included on copies of documents submitted to the Sponsor, the names (except for the initials) must be obliterated and replaced with the assigned study patient numbers.

The principal investigator should keep a separate log of patient identification numbers, names, addresses, telephone numbers and hospital numbers (if applicable). Documents not for submission to the Sponsor, such as signed informed consent forms, should be maintained in strict confidence by the principal investigator in the study site file.

A screening log will be maintained for patients who have been approached to participate in the study and have refused consent or consented to participate in the study but for whatever reason, consent was subsequently withdrawn. This log will contain the following information:

- Patient study number
- Patient initials
- Reason for refusal/withdrawal of consent (if available)
- Other reason(s) for non-inclusion of data (if applicable)

CRF pages will not be completed for these patients.

The investigator shall permit authorised representatives of the Sponsor, regulatory authorities and IECs to review that portion of the patient's medical record that is directly related to the study. As part of the required content of informed consent, the patient must be informed that his/her records will be reviewed in this manner.

6. Management and reporting of adverse events/adverse reactions

Definition of Adverse Events

For the purposes of this study, AEs will be defined as any new diagnosis, any reason for referral to a consultant, any unexpected deterioration in a concurrent illness, any suspected adverse drug reaction, or any complaint which was considered to be of sufficient importance such that it should be recorded in the medical/nursing notes from the point of administration of Ayendi.

The principal investigator will assess the severity of all AEs according to routine practice at the hospital. The investigator will also assess the relationship of AEs to Ayendi using the criteria used during routine clinical practice.

Recording of Adverse Events in the case report form

Only AEs that are recorded in the patient's hospital notes as part of routine clinical practice will be recorded in the CRF.

Information on each AE may include its duration (start and end time and date or ongoing), its frequency (e.g. single episode, intermittent, continuous), its severity (e.g. mild, moderate, severe), a causality assessment (e.g. coexisting disease, concomitant medication, Ayendi, or other cause), its relationship to Ayendi (e.g. unrelated, unlikely, possibly, probably, definitely), whether this influenced the course of the Ayendi treatment, whether it required specific action or therapy, and outcome. The level of information recorded on the CRF is dependent on the information that has been recorded in the patient's ED records.

Reporting of Adverse Events

All adverse event data will be summarised in the Clinical Study Report (CSR).

Serious Adverse Events

In accordance with GVP Module VI, as a non-interventional, observational study which has a design based on the secondary use of data collected from a primary source, expedited reporting to the regulatory authorities (MHRA in this instance) is not required.

Serious Adverse Events (SAEs) will be reported in the Clinical Study Report.

Definition of Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) is defined as one of the following:

- An event that causes the death of the patient.
- A life-threatening* event.
- An event causing hospitalisation** or prolongation of existing hospitalisation.
- An event causing persistent or significant disability or incapacity***.
- An event causing a congenital anomaly or birth defect in the offspring of a woman treated before or during pregnancy.
- Important medical events (i.e., not immediately life-threatening or do not result in death or hospitalisation but require urgent and intensive intervention to prevent one of the outcomes listed in the definition above, for example, intensive treatment at home or in an emergency room for bronchospasm or convulsion)

* The term 'life-threatening' refers to an event in which the patient was at risk of death at the time of event; it does not refer to an event that hypothetically might have caused death if it were more severe.

** A hospitalisation is defined as an overnight stay, including time spent in an emergency room, for an AE. A prolongation of existing hospitalisation is defined as an additional overnight stay. Elective surgery is not classified as an SAE. For the purposes of this study, presentation in an Emergency Department or hospitalisation for the presenting injury will not be considered an SAE unless there is a prolongation to the anticipated duration of hospitalisation for an injury of that nature. Any other unanticipated outcome of the presenting injury that that meets the definition of a serious adverse event should be reported as an SAE

*** The term 'persistent or significant disability or incapacity' refers to an event that results in a substantial or permanent disruption of patient's ability to carry out normal life functions.

7. Plans for disseminating and communicating study results

The Sponsor will prepare a written clinical study report according to ICH guidelines to summarise the study following completion of the analysis.

Investigators may not submit study information for publication without prior consultation and written approval from the Sponsor. However such approval should not be unreasonably withheld. There will be no separate publication policy.

Assessor's comments: this section should identify whether peer review of any intended publication is to be obtained from the MHRA

8. Other comments

Indemnity and Insurance

As a non-interventional, observation only, drug utilisation study, the Sponsor's liability is covered by product liability insurance.

Financial considerations

The study will be financed by Wockhardt UK Limited.
Payments to healthcare professionals for participating in the study shall be restricted to the compensation for time and expenses incurred

9. Assessor's conclusion

This 12 month observational study has been requested by the MHRA and is considered to be a condition of authorisation. This full protocol was submitted following authorisation, following a preliminary assessment of the proposals submitted during the authorisation procedure. The proposed milestones are acceptable, and points that were raised during the initial authorisation procedure have been addressed satisfactorily.

The PASS could be considered acceptable if the following minor points for clarification are addressed:

1. *Given that this study is to be based in a setting where there is experience in the use of intra-nasal administration of diamorphine; information should be obtained as to whether training has been undertaken in the use of Ayendi prior to study start, or whether it has been considered unnecessary. This could be an important variable in order to assess medication error and to consider if there is a need for additional risk management.*
2. *More information should be supplied concerning the data management system* "Syne-clin II"*. Further information should also be provided concerning validation of this system.*
3. *In the analyses it is proposed that stratification will be undertaken, although has not been specific. Stratification should be guided by the two SmPC posologies, and more specific stratification identified. If the data is insufficient to fill the proposed stratifications, then the protocol should describe how they may be altered.*
4. *When communicating and disseminating study results, the protocol should identify whether peer review will be obtained from the MHRA prior to publication.*

10. Assessment of responses

Q1. Data regarding whether the drug administrator has been trained in the use of Ayendi will be collected additionally by the study site nurses on the CRF. The protocol has been updated to reflect this (see Section 9.4 of draft protocol version 0.9.1).

Assessor's comments; the relevant variable has been amended to state "Details (name, position, qualifications, whether training to use Ayendi nasal spray has been undertaken) regarding the Ayendi administrator." This is an important addition to the protocol which can be used to more fully assess final results. **Issue resolved**

Q2. The text provided below regarding the fully validated clinical database data management system, Syne-clin II, has been added as a footer to Section 9.6 of the protocol v0.9.1:

'Syne-clin II is a fully validated MS Access®/SAS based system with validated Open Database Connectivity (ODBC) links to ODBC compliant database management systems e.g. Oracle.

Validation of computer systems at SQN are performed in compliance with the principles of the United Kingdom Statutory Instrument 2004 No. 1031 The Medicines for Human Use (Clinical Trials) Regulations and subsequent amendments, the International Conference on Harmonisation Good Clinical Practice guidelines and the United States Food and Drug Administration Rule 21 CFR Part 11, Electronic Records; Electronic Signatures – Scope and Application.

Details of the validation of Syne-clin II are presented in the table below; the current validation certificate is available as a stand-alone document in Annex I.'

Name of Software	Date software was Implemented	Version of the software/tool that is being used	Licensing Agreement with Software Provider		Hosting the System
Data Management - Syne-clin II in house	1997	5.08/08 Mar 2016	N/A	N/A	In house closed system

The current validation certificate is provided as an addendum to this letter.

Additionally, it has been noted that the method used to perform data consistency reviews was not factually correct and has been changed from manipulation of the data exported to an Excel spreadsheet to the review being undertaken from within the Syne-clin II software. Hence, the text at the end of section 9.6 of the protocol draft version 0.9.1 regarding this review has been amended.

Assessor's comments

Section 9.6 has been amended to include a description of the Syne-clin database system as above within the footnotes, together with certification in annex I. This has resulted in the text flowing between 2 pages but is complete and therefore is satisfactory.

The text regarding consistency reviews has been updated with "Consistency reviews will be performed by data managers directly within Syne-clin II using a series of data validation scripts based on the study validation plan.". This removes reference to excel sheets and provides assurance that the data is contained within a single data management system. **Issue resolved**.

Q3. Section 9.7.1 of the protocol has been revised to include the following more specific details regarding the stratification to be used in the data analysis:

Reporting of the data will be of a descriptive nature and presented using appropriate summary statistics or frequency distributions stratified by age group and weight bands. Unless otherwise stated these tabulations will be supported by data listings.

Age and weight stratifications will be undertaken at the end of the study on the complete dataset. These will be based on the SmPC patient groups in terms of age and weight, as specified in the combined SmPC posologies as well as those patients who are outside the authorised age groups.

The presentation of the age and weight strata will be based on the presentation of summary statistics (e.g. n, mean, SD, %CV, median, minimum, maximum) or frequency distributions (n%). The summaries will be presented if the number of available data points is at least 5. If the number of data points is 4 or less then the summary statistics will only present the sample size (n) and the minimum and maximum values. No percentages less than 1% will be presented for frequency counts but the available sample size (n) will still be presented. As no formal statistical testing is planned there is no requirement to pool stratum comprising small samples of patients. This approach will be fully documented in the SAP.

Assessor's comments: **Issue resolved**

Q4. The protocol has been updated to state that MHRA peer review will be requested prior to publication of any article detailing the study results. (See section 12.3 of draft protocol version 0.9.1).

Assessor's comments: this section has been updated to state "The Sponsor will request peer review by the MHRA of any proposed article detailing the study results before its publication." **Issue resolved**

11. Assessor's final conclusion

This 12 month observational study has been requested by the MHRA and is considered to be a condition of authorisation. All points raised have been addressed satisfactorily.

The PASS is therefore acceptable and approved.