CLINICAL STUDY PROTOCOL

IV – Post authorisation safety study (PASS)

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)**
Short title	**DIAPASS- Ayendi Observational Study**
Study identifier	**DIA003**
Protocol version and Date	**Version 3.0 Dated 23/11/2016**
EU PAS register number	**EUPAS15371**
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(s)	**Wockhardt UK Limited, Ash Road North, Wrexham Industrial Estate, Wrexham, LL13 9UF**
MAH contact person	**Gordon Urquhart, Wockhardt UK Limited**
Joint PASS	**No**
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	**UK**
Author	**Therakind Limited, Third Floor, 314 Regents Park Road,** **London N3 2JX**

1. TABLE OF CONTENTS

1. TABLE OF CONTENTS 2
2. ABBREVIATIONS AND DEFINITIONS 4
3. RESPONSIBLE PARTIES 5
4. ABSTRACT 6
5. AMENDMENTS AND UPDATES 11
6. MILESTONES 11
7. RATIONALE AND BACKGROUND 11
8. RESEARCH QUESTION AND OBJECTIVES 12
8.1 PRIMARY OBJECTIVE 12
8.2 SECONDARY OBJECTIVES 12
9. RESEARCH METHODS 13
9.1 STUDY DESIGN 13
9.1.1 Study Methods 13
9.2 STUDY SETTING 13
9.2.1 Selection of subjects 14
9.3 STUDY SCHEMATIC AND SCHEDULE 15
9.4 VARIABLES AND DATA SOURCES 16
9.5 STUDY SIZE 17
9.6 DATA MANAGEMENT 17
9.7 DATA ANALYSIS 18
9.7.1 Analyses 18
9.7.2 Statistical analysis 19
9.7.3 Quality Control 20
9.8 QUALITY ASSURANCE 20
9.8.1 Study Monitoring 20
9.8.2 Trial Documentation and Storage 20
9.9 LIMITATIONS OF THE RESEARCH METHODS 21
9.9.1 Consideration of potential bias introduced by the consent processes 21
9.10 END OF STUDY 22
10. PROTECTION OF HUMAN SUBJECTS 22
10.1 INFORMED CONSENT 23
10.2 PATIENT CONFIDENTIALITY 23
11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 24

11.1 ADVERSE EVENTS 24
11.1.1 Definition of Adverse Events 24
11.1.2 Recording of Adverse Events in the case report form 24
11.1.3 Reporting of Adverse Events 24
11.2 SERIOUS ADVERSE EVENTS 24
11.2.1 Definition of Serious Adverse Events (SAEs) 25
12 ADDITIONAL CONSIDERATIONS 25
12.1 INDEMNITY AND INSURANCE 25
12.2 FINANCIAL CONSIDERATIONS 25
12.3 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS 26
12.4 INFORMING THE PATIENT OF INCORRECT OR OFF-LABEL USE 26
13. REFERENCES 27
GUIDANCE DOCUMENTS: 27
ANNEX 1. LIST OF STAND-ALONE DOCUMENTS 28
ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS 29
ANNEX 3. PROTOCOL SIGNATURE SHEETS 36
SIGNATURE SHEET 36
SIGNATURE SHEET 37
SIGNATURE SHEET 38
SIGNATURE SHEET 39
SIGNATURE SHEET 40
SIGNATURE SHEET 41
SIGNATURE SHEET 42

2. ABBREVIATIONS AND DEFINITIONS

%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 authorisation
mg	milligram
µg	microgram
MHRA	Medicines & Healthcare products Regulatory Agency
ml	millilitre
µl	microlitre
PASS	Post Authorisation Safety Study
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event
WHO	World Health Organisation

Date at which a study commences: Date of the start of data collection.

Start of data collection: The date from which information on the first study subject is first recorded in the study dataset.

End of data collection: The date from which the analytical dataset is completely available.

Analytical dataset: The minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study.

Substantial amendment to the study protocol: Amendment to the protocol likely to have an impact on the safety, physical or mental well-being of the study participants or that may affect the study results and their interpretation, such as changes to the primary or secondary objectives of the study, to the study population, to the sample size, to the definitions of the main exposure, outcome and confounding variables and to the analytical plan.

3. RESPONSIBLE PARTIES

Sponsor	Wockhardt UK Limited Ash Road North Wrexham LL13 9UF
Co-developer and Project Management	Therakind Limited Third Floor, 314 Regents Park Road, London N3 2JX Tel: 0208 3466035 Fax: 0208 3467305
Chief Investigator	Chief Investigator: Dr Jason Kendall Emergency Department, North Bristol NHS Trust, Southmead Road Westbury-on-Trym Bristol BS10 5NB Tel: 0117 414 4996 Email: Jason.Kendall@nbt.nhs.uk Principal investigators: Principal investigators will be recruited from a wide range of hospital Emergency Departments (EDs) to include teaching and non-teaching hospitals, geographical coverage across the UK, department size, experience with diamorphine, and combined or separate paediatric EDs.
Sponsor's Medical Advisor	Dr Julian Sandell Consultant in Emergency Paediatrics Department of Child Health Poole Hospital NHS Trust Longfleet Road, Poole Dorset BH15 2JB Email: julian.sandell@poole.nhs.uk Tel: 01202 665511 Bleep 0156
Data Management and Statistician	Syne Qua Non Ltd, Gostling House, Diss Business Park, Hopper Way, Sandy Lane, Diss, Norfolk, IP22 4 GT. Tel: +44 (0) 1379 644449 Fax: +44 (0) 1379 644445
Regulatory Compliance	Therakind Limited

Site Management/Monitoring	Therakind Limited
Pharmacovigilance	Wockhardt UK Ltd Drug Safety & Information Department for assessment and reporting in compliance with GVP Module VI & VIII. Wockhardt UK Limited Ash Road North Wrexham LL13 9UF Tel 01978 661261

4. ABSTRACT

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)
STUDY NUMBER:	DIA003
FINAL PROTOCOL DATE:	Draft 3.0 Dated 23/11/2016
PHASE:	IV – Post authorisation safety study (PASS) Drug Utilisation Study (DUS)
SPONSOR:	Wockhardt UK Limited
CHIEF INVESTIGATOR/ STUDY SITES:	Chief Investigator: Dr Jason Kendall Emergency Department, North Bristol NHS Trust, Southmead Road Westbury-on-Trym Bristol BS10 5NB Tel: 0117 414 4996 Email: Jason.Kendall@nbt.nhs.uk <u>Principal Investigators:</u> Principal investigators will be recruited from a wide range of hospital EDs to include teaching and non-teaching hospitals, geographical coverage across the UK, department size, experience with diamorphine, and combined or separate paediatric EDs. Investigators may be physicians, nurse practitioners or suitably experienced researchers. Qualification of all investigators will be documented.
RATIONALE AND BACKGROUND	On review of the marketing authorisation application for Ayendi Nasal Spray 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 ED. 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 risk minimisation activities. **The study is observational with no intervention.**
RESEARCH QUESTION	To evaluate the practical usage of Ayendi Nasal Spray as a treatment post marketing in UK EDs.
OBJECTIVES:	The following information will be collected and evaluated: ▸ Administration setting ▸ Patient characteristics ▸ Dose administered (to evaluate deviations from the prescribing and dosing instructions in the approved Summary of Product Characteristics) ▸ How prescribed and administered, (to evaluate if there are any differences in drug utilisation between the hospitals and prescribers) ▸ Adverse events ▸ Concomitant medication The study will assess patterns of drug utilisation with respect to aspects that may have an impact on its safety (e.g. co-medication [including other opioids], medication errors) and evaluate the effectiveness of risk minimisation activities.
STUDY DESIGN:	Observational Model: Case-Only Time Perspective: Prospective.
STUDY SIZE:	A minimum of 400 patients will be recruited from EDs across a minimum of 20 hospitals (from a wide variety with respect to teaching and non-teaching hospitals, geographical coverage across the UK, department size, experience with diamorphine, and combined or separate paediatric EDs). Each site will aim to recruit a minimum of 10 patients and will be limited to a maximum of 60 patients. The sample size will have sufficient power to estimate both the rate of incorrect dosing and use in association with other opioids The rates 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 patients 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 patients provides precise estimates for a range of rates.
POPULATION - INCLUSION CRITERIA:	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 also 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. 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 applicable, child patients should assent to allow their data to be used for the study.
POPULATION - EXCLUSION CRITERIA:	None
VARIABLES:	Primary Parameters: ▸ Rate (%) of doses given (mg/kg) which deviate from the posology as written in the SmPC. ▸ Patients with previous opioid usage immediately prior to Ayendi (%) Secondary Parameters: ▸ 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 (%)
DATA SOURCES	The attending ED Healthcare Professional will decide if Ayendi Nasal Spray is the optimum pain relief treatment and will administer the drug as per routine clinical practice as appropriate – this is not part of the study. After Ayendi has been administered but before the patient is discharged from the ED, approved hospital staff (including the direct clinical care team and hospital research staff) will approach the parent(s)/legal guardian/patient (whichever is applicable) to discuss the use of the patient's data for research purposes. If the parent(s)/legal guardian(s)/patient (whichever is applicable) agrees to the inclusion of the patient's data in the study, approved hospital staff will transcribe from ED records onto study specific Case Report Forms the following information: ▸ 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, whether training to use Ayendi nasal spray has been undertaken) regarding the Ayendi administrator ▸ Time of dose (if Ayendi administered more than once, time of each separate dose) ▸ Strength and dose of Ayendi prescribed

	▸ Strength and dose administered ▸ Any issues with dosing as per the routine practice in the ED records. ▸ 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 This is purely an observational study and no further information will be documented as part of the study. Information not recorded as part of routine clinical practice should not be included in the CRF, even when available – the CRF is not regarded as primary source data. **Safety Assessments:** Assessments of safety will be performed throughout the time that the patient is in the hospital according to standard ED practice. No further data will be collected regarding the patient once they have left the ED. Adverse event recording Adverse events 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 patient's medical/nursing notes. These data will be transcribed onto the CRF. **Only AEs that are recorded in the patient's hospital notes as part of routine clinical practice will be recorded in the CRF.** Adverse event reporting This is a non-interventional study based on secondary use of data and will be conducted in compliance with GVP Module VIII and VI, where appropriate. As such and in accordance with GVP Module Section VIII.B.6.2 and GVP Module VI Section VI.C.1.2.1., expedited reporting of Serious Adverse Events is not required in this study. All adverse events, including Serious Adverse Events, will be reported in the Clinical Study Report.
STUDY DURATION:	Data collection will be requested for the single visit to the ED.
DATA ANALYSIS:	This is an observational study of patients post receiving prescribed Ayendi Nasal Spray in EDs in order to assess the utilisation of Ayendi post marketing authorisation approval. 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.
MILESTONES:	The study data collection period is estimated to be approximately 12 months from initiation. An interim report will be generated at approximately 6 months. The study report will be available within 12 months of completion of data collection.
DATA SAFETY MONITORING COMMITTEE (DSMC):	None
DATA QUALITY CONTROL:	A minimum 10% sample of CRFs at each participating site will be 100% quality controlled against the source data record.
ADDITIONAL DATA VALIDATION:	<u>Additional, separate, retrospective case study</u> The MHRA have requested confirmatory retrospective data extraction where data will be collected from a second cohort of patients. Additional summary data will be used, to provide validation for the results of the prospective study, to ensure that no bias has been introduced by the consent process. A minimum of 5 sites will provide retrospective, anonymised data extracted from an additional number of patients who have been dosed with the product. The retrospective data extraction will likely begin towards the end of the prospective study when sufficient data are available. The timing and number of patients will be agreed on a site by site basis. Application for approval of this retrospective data extraction will be made separately.
GUIDANCE DOCUMENTS:	▸ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States, Official Journal of the European Communities, 1.5.2001; L 121/34-44. ▸ ICH Topic E 6. Guideline for Good Clinical Practice. Step 5, Consolidated Guideline from 01.05.1996. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Jan.1997. ▸ Statutory Instruments (UK Law): SI 2004 No. 1031, 2006 No 1928. ▸ Guidance for the format and content of the protocol of non-interventional post authorisation safety studies EMA/623947/2012 ▸ Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products. EMA/873138/2011 (superseded version) ▸ Guideline on good pharmacovigilance practices (GVP) Module VIII - Module VIII – Post-authorisation safety studies (Rev 1)
STUDY REGISTRATION:	Therakind Limited will make study information available in the EU electronic register of post-authorisation studies (EU PAS Register). The study protocol

	will be entered in the register before the start of data collection. Updates of the study protocol in case of substantial amendments, progress reports, where applicable, and the final study report will be entered in the register (if possible within two weeks after their finalisation).

5. AMENDMENTS AND UPDATES

None

Number	Date	Section of study protocol	Amendment or update	Reason
-	-	-	-	-

6. MILESTONES

Milestone	**Planned date**
Start of data collection	Estimated at Q4 2016
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

7. 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. 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 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).

8. RESEARCH QUESTION AND OBJECTIVES

The purpose of this prospective observational study is to evaluate the practical usage of Ayendi Nasal spray post authorisation in UK Emergency Departments.

8.1 Primary objective

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 (%)

8.2 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 (%)

9. RESEARCH METHODS

9.1 Study Design

This is an MHRA requested observational, case-only, prospective study into the use of Ayendi Nasal Spray in hospital EDs in order to assess the drug utilisation post marketing authorisation.

No medicinal product will be supplied by the Sponsor; Ayendi will be available already at the hospital pharmacy without reference to this study.

Ayendi will be administered according to clinical need as determined by the attending ED physician – the Sponsor research team will have no influence on which, or even if, patients are prescribed Ayendi.

It is anticipated that Ayendi will be administered to the patient in accordance with the SmPC, although data will be collected on **all** patients who receive Ayendi (where appropriate consent to include their data in the study is obtained) in line with the MHRA requirement for this study (as described in the final assessment report of the marketing authorisation application for Ayendi).

9.1.1 Study Methods

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 – **this is not part of the study**.

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, approved hospital staff (including the direct clinical care team and hospital research nurses) 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, approved 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.

9.2 Study Setting

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.

9.2.1 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 also 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

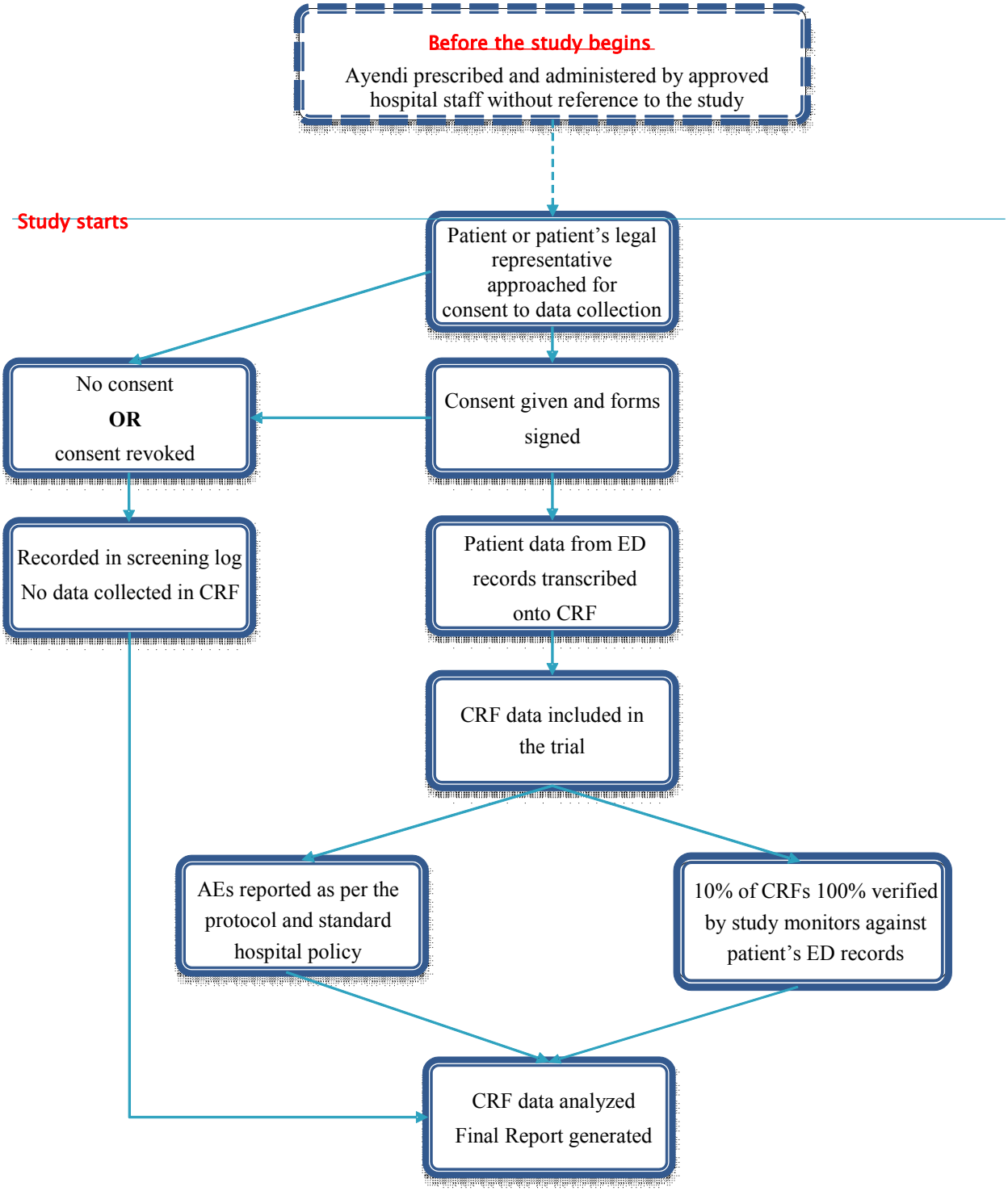
Withdrawal criteria

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.

9.3 Study schematic and schedule

A study schematic is presented below.



9.4 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 approved hospital 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, whether training to use Ayendi nasal spray has been undertaken) regarding 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.

9.5 Study size

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.

9.6 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[1], 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

[1] Syne-clin II is a fully validated MS Access®/SAS based system with validated 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

validate the data post entry. 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.

9.7 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.

9.7.1 Analyses

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.

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.

9.7.2 Statistical analysis

Analysis Populations

Data will be presented for the Safety population, that is, it will include all patients for whom appropriate informed consent was obtained to allow collection of their data.

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.

9.7.3 Quality Control

The database will include data storage tables, entry and edit screens, validation rules and programs, audit trails and tracking systems. For the Tables and Listing validation process, Syne Qua Non will double-programme all the tables and analysis datasets. The listings will be program reviewed by a second programmer. A statistician will perform a high level review of all the tables and listings and checked the output against the final statistical analysis plan (SAP).

9.8 Quality Assurance

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.

9.8.1 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.

9.8.2 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.

9.9 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.

9.9.1 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.

9.10 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.

10. 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.

10.1 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.

10.2 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.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a non-interventional study based on secondary use of data and will be conducted in compliance with GVP Module VIII and VI, where appropriate. As such, and in accordance with GVP Module Section VIII.B.6.2 and GVP Module VI Section VI.C.1.2.1., expedited reporting of Serious Adverse Events is not required in this study.

Assessments of safety will be performed throughout the time that the patient is in the hospital according to standard ED practice. No further data will be collected regarding the patient once they have left the ED.

11.1 Adverse Events

11.1.1 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.

11.1.2 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.

11.1.3 Reporting of Adverse Events

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

11.2 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.

11.2.1 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.

12 ADDITIONAL CONSIDERATIONS

12.1 Indemnity and Insurance

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

12.2 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

12.3 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.

The Sponsor will request peer review by the MHRA of any proposed article detailing the study results before its publication.

There will be no separate publication policy.

12.4 Informing the patient of incorrect or off-label use

In the event that the participants have been prescribed an incorrect dose of Ayendi or they have been prescribed Ayendi "off-label", the medical staff are responsible for ensuring that the participant and/or their legal guardian is informed of this occurrence as per routine policy at the hospital e.g. the error would be assessed for significance by senior staff members in the ED and, depending on the NHS Trust's policy regarding reporting errors of varying levels of significance, the error could be reported through the DATIX electronic system or reported using an "AIMS" (Accident and Incident reporting) form which starts a formal process to evaluate the error, learn from it and put measures in place to prevent recurrence.

In the event that during a monitoring visit, the Sponsor's representative becomes aware of incorrect or off-label use, this will conveyed to the principal investigator at the site as well as being documented in the visit report.

13. REFERENCES

1. DIA001- An open label single dose pharmacokinetic study of Diamorphine Hydrochloride Nasal Spray (0.06mg/kg) in children. EudraCT No: 2009-014983-20
2. DIA002- An open label, single dose safety study of Diamorphine Hydrochloride Nasal Spray (0.1mg/kg) in children. EudraCT No: 2009-014982-16

Guidance documents:

- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States, Official Journal of the European Communities, 1.5.2001; L 121/34-44.
- ICH Topic E 6. Guideline for Good Clinical Practice. Step 5, Consolidated Guideline from 01.05.1996. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Jan.1997.
- Statutory Instruments (UK Law): SI 2004 No. 1031, 2006 No 1928.
- Guidance for the format and content of the protocol of non-interventional post authorisation safety studies EMA/623947/2012
- Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products. EMA/873138/2011 (superseded version)
- Guideline on good pharmacovigilance practices (GVP) Module VIII - Module VIII – Post-authorisation safety studies (Rev 1)

Annex 1. List of stand-alone documents

- Subject information leaflet/informed consent for adult patients
- Subject information leaflet/informed consent for parents
- Subject information leaflet under 8 years
- Subject information leaflet 8-<12 years
- Subject information leaflet 12-<16 years
- Subject assent form for children.
- System validation certificate for Syneclin II, Release 5.08

Annex 2. ENCePP checklist for study protocols

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:	☒	☐	☐	11 (section 7)
1.1.1 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)	☒	☐	☐	12 (section 8)
1.1.2 The objectives of the study?				
1.2 Does the formulation of the research question specify:	☒	☐	☐	13 (section 9)
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☐	☐	☒	
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
1.2.3 if applicable, that there is no *a priori* hypothesis?				

Comments:

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. This will ensure that the population studied is representative of the target population.

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	13 (section 9)
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	11 (section 6)
2.2.2 Age and sex?	☒	☐	☐	13(section 9.2)
2.2.3 Country of origin?	☒	☐	☐	12 (section 8)
2.2.4 Disease/indication?	☐	☐	☒	
2.2.5 Co-morbidity?	☐	☐	☒	
2.2.6 Seasonality?	☐	☐	☒	

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	13(section 9.2)

Comments:

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

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	12(section 8)
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	13(section 9)
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	16(section9.4)
3.4 Is sample size considered?	☒	☐	☐	17(section9.5)
3.5 Is statistical power calculated?	☒	☐	☐	17(section9.5)

Comments:

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.

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:	☒	☐	☐	

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	16(section9.4)
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc)	☐	☐	☒	16(section9.4)
4.1.3 Covariates?				
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	16(section9.4)
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	16(section9.4)
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	18(section9.7)
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	18(section9.7)
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	16(section9.4)

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	15(section9.3)
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	16(section9.4)
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	See comment

Comments:

Objectives page 12 (section 8), Variables measures page 16 (section 9.4). Summary data from a retrospective observational study of unconsented patients, with no personally identifiable details will be used, to provide validation for these results.

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	21(section9.9)
7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	21(section9.9)
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	21(section9.9)
7.4 Does the protocol address other limitations?	☒	☐	☐	21(section9.9)

Comments:

Prior use of opioids is a primary endpoint

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☐	☐	☒	
8.2 Is the choice of statistical techniques described?	☒	☐	☐	18(section 9.7)
8.3 Are descriptive analyses included?	☒	☐	☐	18(section 9.7)
8.4 Are stratified analyses included?	☒	☐	☐	18(section 9.7)
8.5 Does the plan describe the methods for identifying: 8.5.1 Confounders? 8.5.2 Effect modifiers?	 ☐ ☐	 ☐ ☐	 ☒ ☒	
8.6 Does the plan describe how the analysis will address: 8.6.1 Confounding? 8.6.2 Effect modification?	 ☐ ☐	 ☐ ☐	 ☒ ☒	

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	17 (section 9.6)

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.2 Are methods of quality assurance described?	☒	☐	☐	19 (section 9.8)
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	20 (section 9.8)
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	13 (section 9.1)
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	☒	☐	☐	11 (section 6)
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☒	☐	☐	
9.5.3 Study completion?	☒	☐	☐	
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	11(section 5)
9.7 Are communication methods to disseminate results described?	☒	☐	☐	25 (section 12)
9.8 Is there a system in place for independent review of study results?	☒	☐	☐	25 (section 12)

Comments:

9.8 Peer review of publication, submission to MHRA

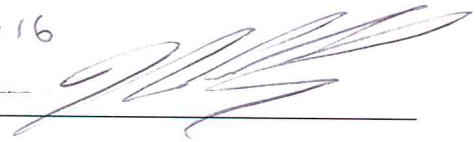
Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	22 (section 10)
10.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	22 (section 10)
10.3 Have data protection requirements been described?	☒	☐	☐	20 (section 9.8)

Comments:

Name of the coordinating study entity[2]: Wockhardt (UK) Limited

Name of (primary) lead investigator[3]: Dr Jason Kendall

Date: 6 /12/ 16

Signature: 

[2] A legal person, institution or organisation which takes responsibility for the design and/or the management of a study. The (primary) lead investigator is the person authorised to represent the coordinating study entity.

[3] A person with the scientific background and experience required for the conduct of a particular pharmacoepidemiological or pharmacovigilance study. The lead investigator is responsible for the conduct of a study at a study site. If a study is conducted at several study sites by a team of investigators, the (primary) lead investigator is the investigator who has overall responsibility for the study across all sites.

Annex 3. Protocol signature sheets

SIGNATURE SHEET

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

SPONSOR

Signed: _____

Mr Gordon Urquhart

Title: European Director Regulatory & Drug Safety (Wockhardt UK Limited)

Date: 5/12/16

SIGNATURE SHEET

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

PROJECT MANAGEMENT

Signed: _____

Dr Susan Conroy

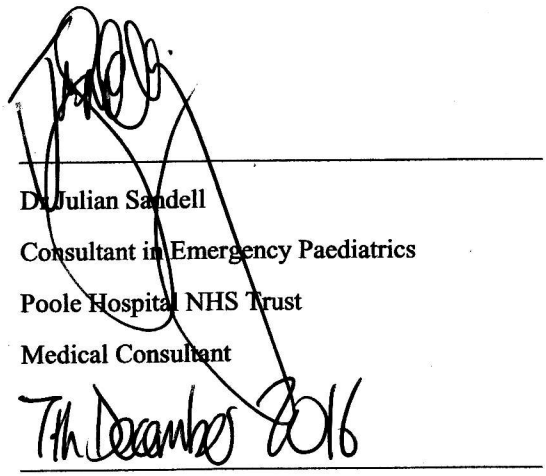
Title: Chief Executive Officer, Therakind Ltd, UK

Date: 05/12/16

SIGNATURE SHEET

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

MEDICAL ADVISOR

Signed: 

Dr Julian Sandell

Consultant in Emergency Paediatrics

Poole Hospital NHS Trust

Title: Medical Consultant

Date: 7th December 2016

SIGNATURE SHEET

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

STATISTICIAN

Signed: _____

Victoria Thomas

Title: Statistician, Syne Qua Non

Date: 5th December 2016

SIGNATURE SHEET

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

REGULATORY COMPLIANCE

Signed: _____

Nicola Howard

Title: Regulatory Compliance Associate, Therakind Ltd, UK

Date: 5 Dec 2016

SIGNATURE SHEET

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

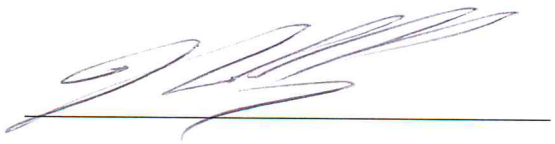
I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and in accordance with the ethical principles of the Declaration of Helsinki and ICH GCP guidelines. I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss the material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will only use the informed consent form approved by the sponsor or its representative and will fulfill all responsibilities for submitting pertinent information to the Independent Ethics Committee (IEC) responsible for the study.

INVESTIGATOR

Address of Institution: Emergency Department,
North Bristol NHS Trust,
Southmead Road
Westbury-on-Trym
Bristol
BS10 5NB

Name: Dr Jason Kendall
Chief Investigator:

Signed: 

Date: 5-12-16

SIGNATURE SHEET

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and in accordance with the ethical principles of the Declaration of Helsinki and ICH GCP guidelines. I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss the material with them to ensure they are fully informed regarding the drug and the conduct of the study.

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INVESTIGATOR

Address of Institution: Individual Signature Pages to be added for each site

Name:

Principal Investigator

Signed: _____

Date: _____