STUDY PROTOCOL

Study title	An observational, real world evidence study to describe clinical experience with lurasidone in the treatment of adult patients with schizophrenia in routine clinical practice in Europe.
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Protocol version	4.0
Date	25 October 2019

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List of abbreviations

Abbreviation	Definition
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate transaminase
CGI-S	Clinical Global Impression, Severity Scale
CI	Confidence interval
CL	Confidence limit
DCF	Data collection form
EDC	Electronic data capture
eDCF	Electronic data collection form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
GGT	Gamma glutamyl transpeptidase
HDL	High density lipoprotein
HRA	Health Research Authority
IEC	Independent Ethics Committee
IQR	Interquartile range
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LDL	Low density lipoprotein

MADRS	Montgomery–Asberg Depression Rating Scale
PANSS	Positive and Negative Syndrome Scale
NHS	National Health Service
NICE	National Institute for Heath and Care Excellence
R&D	Research and Development
REC	Research Ethics Committee
SD	Standard deviation
SGA	Second generation antipsychotic
UK	United Kingdom

1. Key definitions

Index event: Initiation (first prescription) of lurasidone

Index event date: Date of initiation of Lurasidone

Baseline: Baseline is defined as the closest measurement taken within 3 months prior to index event.

Pre-index observation period: This will extend from the date of diagnosis of schizophrenia up to the index event.

Post-index observation period: This will extend to a maximum of 12 months post index event.

Permitted windows for endpoints related to specific time points: Where measurements closest to the 3, 6, 9, and 12 month time point after index event are to be analysed, the closest measurement must fall within 4 weeks either side of each time point.

Schizophrenia Relapse: Relapse of schizophrenia will be defined according clinician's judgement as recorded in patients' medical records.

2. Study abstract

Title	An observational, real world evidence study to describe clinical experience with lurasidone in the treatment of adult patients with schizophrenia in routine clinical practice in Europe.
Rationale for study	Lurasidone is a second generation antipsychotic agent that has been shown to have a lower risk of weight gain and is associated with a lower incidence of metabolic adverse events in comparison to other drugs of the same therapeutic class in patients with schizophrenia. However, there is currently a paucity of real world evidence in Europe on the effectiveness of lurasidone treatment and its position in the treatment pathway for schizophrenia. This observational study aims to address this knowledge gap.
Research question and hypothesis	• What treatments for schizophrenia do adult patients receive in routine clinical practice, prior to initiation with lurasidone treatment? • What are the baseline demographic and clinical characteristics of patients with schizophrenia treated with lurasidone in routine clinical practice? • What is the current position of lurasidone in the treatment pathway for schizophrenia? • What is the dosing regimen and titration profile of lurasidone used in patients with schizophrenia? • What proportion of patients discontinue lurasidone treatment within 12 months and what are the reasons for discontinuation? • What outcomes and related adverse events are seen in patients in the 12 months after initiation of lurasidone? • What healthcare resources are utilised by patients with schizophrenia in the first 12 months after initiation of lurasidone?
Objectives	**Primary objective** • To describe the dose titration process, dosing regimens, treatment duration and reasons for discontinuation following initiation of lurasidone in adult patients with schizophrenia. **Secondary objectives** • To describe the treatment history of adult patients with schizophrenia prior to initiation of lurasidone in routine clinical practice. • To describe baseline demographics and clinical characteristics of adult patients with schizophrenia commencing treatment with lurasidone. • To describe the position of lurasidone within the treatment pathway for adult patients with schizophrenia. • To describe the clinical outcomes of patients over 12 months from the date of initiation of lurasidone. • To describe the adverse events related to lurasidone treatment observed over the 12 months from data of initiation in adult patients with schizophrenia. • To describe healthcare resource utilisation for patients over 12 months from the date of first initiation of lurasidone.

Study design	This is an international, multi-centre observational study based on both retrospective and prospective collection of data from patients' medical records, to be conducted in mental health centres in the United Kingdom (UK), Netherlands and Switzerland. It is a single group study without a comparator, to reflect real world clinical practice. There will be no changes to patient management for the purposes of any part of the study and no additional tests, investigations or visits will be required. Patients prescribed lurasidone in routine clinical practice will be identified by members of their care team and (if living) approached and asked to provide consent for their medical records to be used in the study.
Setting	This study will be conducted in 4 to 8 mental health centres in the United Kingdom (UK), Netherlands and Switzerland.
Participants	The target sample size for this study is 80 patients receiving treatment with lurasidone in mental health centres in the UK, Netherlands and Switzerland. **Inclusion criteria** 1. Aged ≥18 years of age at time of initiation of lurasidone. 2. Provided consent for access to medical records for study data collection (applicable to living patients only). 3. Documented diagnosis of schizophrenia before the initiation of lurasidone. 4. Initiated on lurasidone after the 01st January 2016. 5. Judged to have capacity by their clinician to provide valid written informed consent to participate on this study. **Exclusion criteria** 1. Patients whose medical records are unavailable for review. 2. Patients who participated in a clinical trial of an investigational medicinal product during the post-index observation period. **Participant selection** Eligible patients who provide written informed consent will be included in the study. Deceased patients may still be eligible for participation but cannot provide informed consent. To avoid causing distress to relatives and next of kin of deceased patients, consent will not be sought for use of data. Instead, data from deceased patients will be collected by members of the direct care team who have a right to access medical records healthcare.
Data source(s)	Data will be sourced from patients' medical records (paper and/or electronic, as applicable locally) and other electronic systems within each study centre (e.g. laboratory records, electronic investigations systems, prescription records).

Study time period(s)	The pre-index observation period of this study will extend from the date of diagnosis of schizophrenia up to the date of initiation of lurasidone treatment (the index date). All data to be collected in the pre-index observation period will be recorded but only if there is documented record of the data in the medical records within the 10 years prior to the index date. Baseline patient characteristics and observations will be collected within 3 months prior to the index date. The post-index observation period will extend up to 12 months after the index date.

Study endpoints	**Primary Endpoint**
	• Summary measures of lurasidone treatment duration i.e. Proportion of patients taking treatment for full 12 months
	Secondary Endpoints
	• Summary measures of baseline demographics
	• Summary measures of baseline clinical characteristics and comorbidities
	• Summary measures of treatment history for schizophrenia (from date of diagnosis to index date) including:
	  • Duration of disease until Index date
	  • Prior treatments for schizophrenia
	  • Distribution of reasons for treatment changes
	• Dose distribution of lurasidone prescribed to patients with schizophrenia during the study observation period
	• Summary measures of starting and subsequent doses of lurasidone
	• Summary of lurasidone treatment discontinuations
	• Reasons for initiation of lurasidone
	• Reasons for dose changes of lurasidone
	• Reasons for discontinuation of lurasidone
	• Distribution of patients taking lurasidone in the morning or evening
	• Distribution of patients taking lurasidone with a meal
	• Summary distribution of concomitant anti-psychotic medications
	• Summary distribution of other therapies for schizophrenia
	• Number of treatments for schizophrenia prior to initiation of lurasidone
	• Number of new treatments for schizophrenia after discontinuation of lurasidone (during post-index observation period)
	• Time until first relapse in the 12 months following initiation of lurasidone
	• Number of relapses in the 12 months following initiation of lurasidone
	• Adverse events following the initiation of lurasidone

	• Changes in weight, blood glucose, lipid levels, and liver function from baseline at approximately 3, 6, 9 and 12 months (±1 month) following the initiation of lurasidone
	• Summary measures of healthcare resource utilization following initiation of lurasidone to include:
	  • Inpatient admissions per patient, including specialty, elective or non-elective and reasons
	  • Inpatient bed days per patient
	  • Length of stay per inpatient admission
	  • Outpatient visits per patient
	  • Emergency department visits per patient

3. Study amendments and protocol deviations

All amendments to the protocol will be documented in Table 1.

Protocol deviations will be documented in a Protocol Deviation Log (maintained in a separate document).

Table 1. Study amendments

Amendment number	Date of amendment	Section amended	Amendment description	Reason for amendment
1	18-SEP-18	Synopsis Section 7 Section 11	Amended eligibility criteria and pharmacovigilance reporting address	To meet UK ethics committee requirements and adverse event reporting requirements.
2	25-OCT-19	Title page Section 11	Contact details (Real World Evidence Consultant) updated Pharmacovigilance reporting address	To meet ethics committee requirements and adverse event reporting requirements.
3				
4				

4. Milestones

Table 2. Study milestones

Study timelines will be updated and monitored during study development and set up.

Timelines set below are indicative only and not finite.

Milestone	Planned date(s) United Kingdom	Planned dates(s) Netherlands	Planned date(s) Switzerland
Planned start of study	OCT-2018	NOV-2018	NOV-2018
Planned collection of first data point	DEC-2018	DEC-2018	DEC-2018
Planned collection of last data point	AUG-2019	AUG-2019	AUG-2019
Study progress report 1	SEP-2019	OCT-2019	OCT-2019
Interim study report 1	MAR-2019	MAR-2019	MAR-2019
Registration in EU Post-authorisation study Register or equivalent public database	OCT-2018	OCT-2018	OCT-2018
Final report of study results (end	NOV-2019	NOV-2019	NOV-2019

of study)			

5. Background

Schizophrenia is a complex disorder requiring long term antipsychotic treatment for adequate management of symptoms and prevention of relapse(1). The incidence rate for schizophrenia has been reported to be from 7.7 to 43.0 per 100,000(2). Treatment for schizophrenia includes both pharmacological treatments and psychotherapy. Second generation anti-psychotics (SGAs) are generally the first line of pharmacological treatment for schizophrenia and are preferred over first generation anti-psychotics as they cause fewer extrapyramidal adverse effects like akathisia, dyskinesia and dystonia(1). However, SGAs are associated with several adverse effects (weight gain, metabolic syndrome, akathisia) and their prescription requires careful consideration of patients' previous tolerability, clinical history and comorbidities(3–5).

Lurasidone is a SGA that has been shown to have a lower risk of weight gain and is associated with a lower incidence of metabolic adverse events in comparison to some other drugs of the same therapeutic class(6–9). A recent retrospective analysis of an electronic prescription database in the USA reported that lurasidone treatment for patients with schizophrenia and bipolar disorder was associated with a reduction in body weight during the first year of treatment(10). Long term treatment with lurasidone has also been associated with lower incidence of disease relapse(11). Lurasidone received a marketing authorisation from the European Medicines Agency (EMA) in 2014.

5.1. Rationale for the study

There is currently a paucity of real world evidence in Europe on the effectiveness of lurasidone treatment and its position in the treatment pathway for Schizophrenia. This study aims to address this knowledge gap by describing the baseline patient demographics, clinical characteristics and adverse events as well as clinical outcomes such as changes in body weight and metabolic parameters observed during the first twelve months following initiation of lurasidone treatment.

6. Research question(s), hypothesis and objectives

6.1. Research question and hypothesis

- What treatments for schizophrenia do adult patients receive in routine clinical practice, prior to initiation with lurasidone treatment?
- What are the baseline demographic and clinical characteristics of patients with schizophrenia treated with lurasidone in routine clinical practice?
- What is the current position of lurasidone in the treatment pathway for schizophrenia?
- What is the dosing regimen and titration profile of lurasidone used in patients with schizophrenia?
- What proportion of patients discontinue lurasidone treatment within 12 months and what are the reasons for discontinuation?
- What outcomes and related adverse events are seen in patients in the 12 months after initiation of lurasidone?
- What healthcare resources are utilised by patients with schizophrenia in the first 12 months after initiation of lurasidone?

6.2. Primary objective

To describe the dose titration process, dosing regimens, treatment duration and reasons for discontinuation following initiation of lurasidone in adult patients with schizophrenia.

6.3. Secondary objectives

- To describe baseline demographics and clinical characteristics of adult patients with schizophrenia commencing treatment with lurasidone.
- To describe the treatment history of adult patients with schizophrenia prior to initiation of lurasidone in routine clinical practice.
- To describe the position of lurasidone within the treatment pathway for adult patients with schizophrenia.
- To describe the clinical outcomes of patients over 12 months from the date of initiation of lurasidone.

- To describe the adverse events related to lurasidone treatment observed over the 12 months from data of initiation in adult patients with schizophrenia.
- To describe healthcare resource utilisation for patients over 12 months from the date of first initiation of lurasidone.

7. Research methods

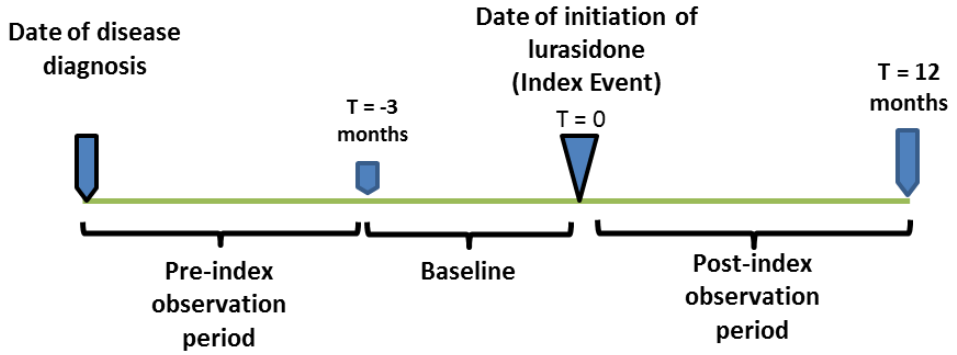
This study has been designed and will be conducted according to the requirements of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; http://www.encepp.eu/index.shtml) and International Society for Pharmacoepidemiology (ISPE; https://www.pharmacoepi.org/resources/guidelines_08027.cfm) guidance, as appropriate.

7.1. Study design

This is an international, multi-centre observational study based on both retrospective and prospective collection of data from patients' medical records, to be conducted in mental health centres in the United Kingdom (UK), Netherlands and Switzerland. It is a single group study without a comparator, to reflect real world clinical practice. Both retrospective and prospective methods of patient identification and consent will be used, as described in section 7.4.3. There will be no changes to patient management for the purposes of any part of the study and no additional tests, investigations or visits will be required. **Error! Reference source not found.** outlines the study design and key data points. A complete list of data variables that will be collected at various time-points of the study are described in section 7.7.

The study design with a twelve month enrolment period will allow for the identification and recruitment of sufficient numbers of participants who have either commenced treatment with lurasidone.

Figure 1: Study design and key data points



Lurasidone received marketing authorization from the EMA in 2014(12). Based on feasibility assessments, data required to evaluate the treatment history, baseline demographics and clinical characteristics of patients with schizophrenia initiated with lurasidone treatment are likely to be routinely recorded for all patients. A twelve month post-index observation period is considered to be a sufficient length of time to capture changes in lurasidone dosage, frequency of schizophrenia relapses and adverse events.

Based on the sample size (80 patients), geographic spread (UK, Netherlands and Switzerland) and patient selection criteria, it is anticipated that the results of this study should be generalisable to the wider patient population with schizophrenia treated with lurasidone in routine clinical practice.

7.2. Setting

This study will be conducted in approximately 1 to 2 mental health centres in each country (UK, Netherlands and Switzerland) that are known to prescribe lurasidone to adult patients with schizophrenia. The selected study centres will be those that are likely to contribute the greatest number of eligible patients to the study.

7.3. Study time periods

The pre-index observation period of this study will extend from the date of diagnosis of schizophrenia up to the date of initiation of lurasidone treatment (the index date). All data to be collected in the pre-index observation period will be recorded but only if there is documented record of the data in the medical records within the 10 years prior to the index date.

Baseline patient characteristics and observations will be collected within 3 months prior to the index date.

The post-index observation period will extend up to 12 months after the index date.

Study enrolment and the entire study duration will depend on the rate of prescription of lurasidone in normal clinical practice at the participating study centres. Study timelines will be updated and monitored during study development and set up.

7.4. Study population

Patients fulfilling the following criteria will be potentially eligible for inclusion in the study:

7.4.1. Inclusion criteria

1. Aged ≥18 years of age at time of initiation of lurasidone.
2. Provided consent for access to medical records for study data collection (applicable to living patients only).
3. Documented diagnosis of schizophrenia before the initiation of lurasidone.
4. Initiated on lurasidone after the 1st January 2016.
5. Judged to have capacity by their clinician to provide valid written informed consent to participate on this study.

7.4.2. Initiated on lurasidone since the 01st January 2016.Exclusion criteria

1. Patients whose medical records are unavailable for review.
2. Patients who are participated in a clinical trial of an investigational medicinal product during the post-index observation period.

The inclusion and exclusion criteria specified above are not expected to materially affect the ability to meet the target sample size within the required timelines.

7.4.3. Patient identification, sampling and recruitment

Patients prescribed lurasidone who meet the study eligibility criteria will be identified by members of their direct care team. Living patients will be approached and asked to provide consent for their medical records to be used in the study.

To enable the target sample size to be achieved two methods of patient identification and consent will be used:

1. Retrospective recruitment: All patients who have been previously initiated on lurasidone at least 12 months before the date of enrolment in the participating centres will be identified from hospital pharmacy records, hospital databases, electronic prescribing records, clinic lists or by review of patient medical records. Living patients will be approached, given information about the study and asked to complete a consent form either by post or when they attend for a routine appointment. Deceased patients may still be eligible for participation but cannot provide informed consent. To avoid causing distress to relatives and next of kin, consent will not be sought for use of data. Instead, data from deceased patients will be collected by members of the direct care team who have a right to access medical records healthcare.
2. Prospective recruitment: Patients who have been initiated on lurasidone less than 12 months before the date of enrolment (i.e. for whom the full 12 month post-index period has not yet elapsed) will be identified from hospital pharmacy records, hospital databases, electronic prescribing records, clinic lists, review of patient medical records or at routine appointments. These patients will be approached, given information about the study and asked to complete a consent form either by post or when they attend for a routine appointment. Consecutive patients will be recruited until the required sample size is achieved.

7.5. Data collection

Data will be collected from medical records both retrospectively and prospectively using a standardised electronic data collection form (eDCF) designed specifically for the study. Data will be collected by members of the direct care team or external researchers via an electronic data capture (EDC) system using eDCFs. Data from deceased patients will be collected by members of the direct care team only to preserve confidentiality. Patients will be identified

in all study records by a unique study code to link multiple study records for each participant (if applicable) and to preserve patient confidentiality.

7.6. Data source

Baseline patient demographic and clinical characteristics, details of lurasidone treatment, healthcare resource utilisation, adverse events and clinical outcomes will be sourced from patients' medical records and other systems within each study centre (e.g. laboratory records, electronic investigations systems, prescription records).

7.7. Study endpoints and dataset

The study endpoints and dataset required to address the study objectives are summarised in Table 3. Study endpoints will be reported using descriptive statistics of distribution, central tendency and dispersion as appropriate for the data collected (as outlined in Section 8). The different study time points at which various data variables will be collected are summarised in Annex 1.

Table 3. Endpoints and dataset required to address the study objectives

Endpoint(s) and variables required to address the primary objective:	
Endpoint to address the primary objective	**Variables required to address the primary objective**
To describe the dose titration process, dosing regimens, treatment duration and reasons for discontinuation following initiation of lurasidone in adult patients with schizophrenia.	
• Summary measures of lurasidone treatment duration (primary endpoint) • Summary of reasons for initiation of lurasidone • Dose distribution of lurasidone prescribed to patients with	• Date of initiation of lurasidone (Index date) (DD/MM/YYYY) • Reason for initiation of lurasidone • Total daily dose of lurasidone at initiation • Dosing regimen of lurasidone at initiation (e.g. once daily, twice daily etc.) • Time of day dose of lurasidone is taken (MM:HH) or am/pm

Endpoint(s) and variables required to address the primary objective:	
Endpoint to address the primary objective	**Variables required to address the primary objective**
To describe the dose titration process, dosing regimens, treatment duration and reasons for discontinuation following initiation of lurasidone in adult patients with schizophrenia.	
schizophrenia during the study observation period • Summary measures of starting and subsequent doses of lurasidone • Summary of reasons for lurasidone dose changes • Summary of lurasidone treatment discontinuations • Summary of reasons for discontinuation of lurasidone • Distribution of patients taking lurasidone in the morning or evening • Distribution of patients taking lurasidone with a meal	• Lurasidone commonly taken with a meal (Yes/No/not recorded) • Stop date of each dose of lurasidone throughout the observation period (DD/MM/YYYY) • Date of initiation of each subsequent new dose of lurasidone (DD/MM/YYYY) • Total daily dose of each subsequent new dose of lurasidone • Dosing regimen of each subsequent new dose of lurasidone (e.g. once daily, twice daily etc.) • Reason for dose change/discontinuation of lurasidone

Endpoint(s) and variables required to address the secondary objectives:	
Endpoint to address the secondary objective	**Variables required to address the secondary objective**
To describe baseline demographics and clinical characteristics of adult patients with schizophrenia commencing treatment with lurasidone	
• Summary measures of baseline demographics • Summary measures of baseline clinical characteristics and comorbidities	• Month and year of birth (MM/YYYY) • Sex (M/F) • Diagnosis of subtype of schizophrenia (paranoid, disorganized, catatonic, undifferentiated, residual,

	schizoaffective disorder or other specify), if recorded • Height (cm), date of measurement (DD/MM/YYYY) • Weight (Kg), date of measurement (DD/MM/YYYY) • BMI, date of measurement (DD/MM/YYYY) • Ethnicity (based on but not exclusive to the following categories: White, Mixed / Multiple ethnic groups, Asian, Black / African / Caribbean /, Other ethnic group) • A current history of alcohol misuse (Y/N) *(defined as a patient who is known to have a current history of drinking excessively more than the lower risk limits of alcohol consumption)* • A current history of illicit drug abuse (Y/N) *(defined as a patient who is known to have a current history of taking illicit substances or drugs)* • Smoking status (Y/N) • Positive and Negative Syndrome Scale (PANSS) total score at baseline • Clinical Global Impression (CGI) severity score at baseline • Montgomery–Asberg Depression Rating Scale (MADRS) total score at baseline • Related Comorbidities o major depressive disorder o substance abuse o hypertension o hyperlipidemia o diabetes o chronic obstructive pulmonary disease o Anxiety • Blood glucose (mg/dl)

	• Serum lipids (Total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], triglycerides) • Liver function test results (Albumin, ALT, ALP, AST, GGT)
To describe the treatment history of adult patients with schizophrenia prior to initiation of lurasidone in routine clinical practice.	

• Summary measures of treatment history for schizophrenia (from date of diagnosis to index date) including:
  ○ Duration of disease until Index date
  ○ Prior treatments for schizophrenia
• Distribution of reasons for treatment changes
	• Date of diagnosis of schizophrenia (DD/MM/YYYY)
	• Date of initiation of lurasidone (DD/MM/YYYY)
	• Names of all prior anti-psychotic treatments and other therapies (cognitive behavioural therapy, compliance therapy, individual supportive therapy) for schizophrenia (pre-index period)
	• Dates of initiation of each prior anti-psychotic treatment and other therapies for schizophrenia before index date (DD/MM/YYYY)
	• Reason for initiating each prior anti-psychotic treatment or other therapy for schizophrenia before index date

To describe the position of lurasidone within the treatment pathway for adult patients with schizophrenia.	
• Summary distribution of concomitant anti-psychotic medications • Summary distribution of other therapies for schizophrenia • Number of treatments for schizophrenia prior to initiation of lurasidone • Number of new treatments for schizophrenia after discontinuation of	• Date of initiation of lurasidone (DD/MM/YYYY) • Names of all prior anti-psychotic treatments and other therapies (cognitive behavioural therapy, compliance therapy, individual supportive therapy) for schizophrenia (pre-index period) • Dates of initiation of each prior anti-psychotic treatment and other therapies for schizophrenia before index date (DD/MM/YYYY)

lurasidone (during post-index observation period)	• Reason for initiating each prior anti-psychotic treatment or other therapy for schizophrenia before index date • Names of anti-psychotic treatments and other therapies (cognitive behavioural therapy, compliance therapy, individual supportive therapy) for schizophrenia following initiation of lurasidone (post-index period) • Dates of initiation of each anti-psychotic treatment and other therapies for schizophrenia following the initiation of lurasidone (DD/MM/YYYY) • Reason for initiating each anti-psychotic treatment or other therapy for schizophrenia following the initiation of lurasidone
To describe the clinical outcomes of patients over 12 months from the initiation of lurasidone.	
• Time until first relapse in the 12 months following initiation of lurasidone • Number of relapses in the 12 months following initiation of lurasidone • Changes in weight, blood glucose, lipid levels, and liver function from baseline at approximately 3, 6, 9 and 12 months (±1 month) following the initiation of lurasidone	• Dates of first relapse of schizophrenia, as documented in the medical records • Dates of subsequent relapses of schizophrenia • Body weight (Kg) and date of measurement (DD/MM/YYYY) • Blood glucose (mg/dl) and date of measurement (DD/MM/YYYY) • Serum lipids (Total cholesterol, LDL, HDL, triglycerides) and date of measurement (DD/MM/YYYY) • Liver function test results (Albumin, ALT, ALP, AST, GGT) and date of measurement (DD/MM/YYYY)
To describe the adverse events related to lurasidone treatment observed over the 12 months from data of initiation in adult patients with schizophrenia.	
• Summary distribution of adverse events following the initiation of lurasidone	• Name and date (DD/MM/YYYY) of adverse event judged to be related to the use of lurasidone if recorded in medical notes

<table>
<tr><td colspan="2">To describe healthcare resource utilisation for patients over 12 months from the date of first initiation of lurasidone.</td></tr>
<tr><td>• Summary measures of schizophrenia-related healthcare resource utilisation following initiation of lurasidone to include:
o Inpatient admissions per patient, including specialty, elective or non-elective and reasons
o Inpatient bed days per patient
o Length of stay per inpatient admission
o Outpatient visits per patient
o Emergency department visits per patient</td><td>• Date of hospital admission for a schizophrenia-related event (DD/MM/YYYY)
• Reason for hospital admission
• Date of discharge from hospital for a schizophrenia-related event (DD/MM/YYYY)
• Speciality department for hospital admission
• Elective/non-elective admission to hospital
• Date of admission to emergency department for a schizophrenia related event (DD/MM/YYYY)
• Date of discharge from emergency department for a schizophrenia related event (DD/MM/YYYY)
• Date of schizophrenia outpatient visits (DD/MM/YYYY)</td></tr>
</table>

7.8. Data management

Data management for eDCFs will be carried out using MACRO™, a data management system which has a secure web-based data entry interface and is fully validated and compliant with Food and Drug Administration (FDA) Information Governance standard 21 Code of Federal Regulations (CFR) part 11(13). The MACRO™ system has restricted access permissions for data entry management and analysis and maintains an audit trail of all changes to data and activity in the system in line with 21 CFR part 11. Entry to MACRO™ will be restricted (by password protection) to only those members of staff directly involved with the study.

7.9. Data quality checks

All data collectors will be provided with Data Collection Guidelines to facilitate consistent completion of the eDCF. The accuracy and quality of data collection via the eDCF will be monitored by reference to source data (source data verification [SDV]). SDV will be performed by external researcher from the study management company on the complete dataset of a random sample of at least 10% of patients at each centre. Any issues identified related to quality, accuracy or consistency of data collection will be discussed with the data collector concerned and further training provided if required. If any subsequent issues are identified related to quality, accuracy or consistency of data collection, a random check of a further 10% of data collected by that data collector will be undertaken. Should any further issues be identified, 100% SDV will be undertaken at the centre. It is the Investigator's responsibility to ensure the accuracy of the data entered in the DCFs.

SDV will be performed by a researcher who did not collect data for that patient record.

As consent for access to medical records by an external researcher cannot be obtained from deceased patients, SDV for deceased patients will be performed using a ‘back-to-back’ methodology with a member of the direct care team. This will involve the direct care team member at site reciting data from the patient notes to the external researcher so that they can verify the data in the eDCF without the need to look directly at the identifiable source records.

All clinical data submitted in the eDCF will be checked for eligibility, completeness and accuracy and queries will be raised by the data management team from the study management company using agreed manual and programmed validation checks. Study

centres will be required to co-operate with the data management team in the resolution of these queries.

8. Statistical methods and sample size estimation

8.1. Sample size estimation

This study's primary endpoints, duration of time to index, treatment history and distribution of reasons for changing treatment, are all fundamentally descriptive in nature. The latter two may be expressed as categorical variables (for instance, the number or percentage of patients with a treatment or the number changing treatment for a particular reason). Given a proposed sample size of 80 (and showing the samples of 50 and 100 patients), 95% confidence intervals (that is an interval around the sample proportion with 95% chance of containing the true proportion for the population) can be seen in Table 4 below across a range of hypothetically possible proportions of patients having different past treatments or reasons for changing treatment.

Table 4. Precision of estimates of proportions for secondary categorical endpoints

Proportion of subjects with endpoint	50 patients		80 patients		100 patients	
	LCL	UCL	LCL	UCL	LCL	UCL
5%	0.8%	15.2%	1.4%	12.3%	1.6%	11.3%
10%	3.3%	21.8%	4.4%	18.8%	4.9%	17.6%
15%	6.5%	27.9%	8.0%	24.7%	8.6%	23.5%
20%	10.0%	33.7%	11.9%	30.4%	12.7%	29.2%
25%	13.8%	39.3%	16.0%	35.9%	16.9%	34.7%
30%	17.9%	44.6%	20.3%	41.3%	21.2%	40.0%
35%	22.1%	49.8%	24.7%	46.5%	25.7%	45.2%
40%	26.4%	54.8%	29.2%	51.6%	30.3%	50.3%
45%	30.9%	59.7%	33.8%	56.5%	35.0%	55.3%
50%	35.5%	64.5%	38.6%	61.4%	39.8%	60.2%
55%	40.3%	69.1%	43.5%	66.2%	44.7%	65.0%
60%	45.2%	73.6%	48.4%	70.8%	49.7%	69.7%

65%	50.2%	77.9%	53.5%	75.3%	54.8%	74.3%
70%	55.4%	82.1%	58.7%	79.7%	60.0%	78.8%
75%	60.7%	86.2%	64.1%	84.0%	65.3%	83.1%
80%	66.3%	90.0%	69.6%	88.1%	70.8%	87.3%
85%	72.1%	93.5%	75.3%	92.0%	76.5%	91.4%
90%	78.2%	96.7%	81.2%	95.6%	82.4%	95.1%
95%	84.8%	99.2%	87.7%	98.6%	88.7%	98.4%

LCL: lower 95% confidence limit; UCL: upper 95% confidence limit

It can be seen from the above table that the confidence interval width narrows with increasing sample size, but also as proportions measured get nearer to 0 or 100%. In one prior study, the percentage of patients using anti-depressants as a prior medication was slightly over 55%(10). For a sample size of 80, if the number of the number of patients with anti-depressants as a past treatment was shared by 55% of the study sample, the 95% confidence interval calculated would range between 43.5 and 66.2%. In the same study, the proportion of patients using diuretics as a prior treatment was approximately 20%. For a recorded rate of 20%, the 95% confidence interval would range between 11.9 and 30.4% for this sample size. Increasing the sample size by 20 would not decrease the size of these intervals under these two scenarios substantially (the intervals would be 44.7% to 65.0% and 12.7 to 29.2% for estimates of 55% and 20% respectively), although decreasing the sample size by 30 would widen the 95% confidence interval widths by more than 5%.

A clinical trial comparing lurasidone to a placebo group found that recruited patients with diagnosed schizophrenia and experience of an acute exacerbation had a mean disease duration of between 16-18 years in each study group with a standard deviation of just under 12 in each case(14). Taking these numbers, we can calculate that we could expect 95% confidence intervals either side of an estimate of 17 years to be between 14.3 and 19.7 with a sample size of 80. For sample sizes of 50 and 100, these intervals would be 13.6 to 20.4 and 14.6 to 19.4 respectively.

8.2. Data analysis plan

All primary endpoint (and secondary endpoint) analyses will be descriptive in nature. For continuous variables (such as duration of time with disease) the mean, standard deviation, median, interquartile range and range will be calculated. For nominal variables (e.g. number of patients receiving a given past treatment or discontinuing for a specific reason), frequencies and proportions in the form of percentages will be calculated for each group. For investigating changes in weight, blood glucose, lipid levels and liver function from baseline at 3,6,9 and 12 months following initiation of lurasidone, changes will be described using summary measures as described for continuous variables above for each time; they will then be compared using a paired t-test (or Wilcoxon signed rank test if distributions are non-normal), although based upon a previous study of changes in weight(10) as a result of treatment change, it is expected that any change will be too small to detect a significant change with a feasible sample size for the study (for a change in weight of -0.77kg over a year with a standard deviation of 25.4, there would only be a power of approximately 5% with the current proposed sample size of 80; a sample of 16,000 per group would be needed for 80% power).

Please note, all percentages will be reported to the nearest whole number; therefore, in reporting study results in tables, figures and associated text, percentages may not add up to 100% due to rounding. For group/subgroup sizes of less than 10, percentages will not be reported, except under exceptional circumstances.

8.3. Missing data

Where data are missing from the original medical record, the affected analyses will be conducted using only the results of those patients with data available and the number included in each analysis will be stated. The percentage of data missing will be reported for each study variable. Where dates are ambiguous because of missing day and/or months, standard imputation will be applied: where day is missing the 15th of the month will be assumed; where both day and month are missing the 1st July will be assumed.

8.4. Subgroup analyses

No subgroup analyses are planned.

8.5. Interim analyses

An interim analysis is planned for this observational study and will take place once a full dataset has been collected for 40 enrolled patients. The interim analysis will be performed by pH Associates and will follow the same analysis plan as the final analysis on the complete study cohort.

8.6. Sensitivity analyses

No sensitivity analyses are planned.

9. Study limitations related to study design

- Patient consent is a requirement of this study for living patients; this may introduce selection bias and result in a study sample that may not be representative of the wider patient population of interest.
- The interpretation of data collected retrospectively will be dependent on the completeness and quality of the medical records and the reliability of the abstraction of data from the medical records. However, SDV will be employed to identify and correct abstraction errors. It is expected that data for the primary endpoint will be well-documented
- Participating centres are those identified as high prescribers so may not be representative of all centres who prescribe lurasidone in the countries of study.
- We have specified that outcomes will be evaluated at 3, 6, 9, 12 months but real world response assessment may differ in terms of the timing of evaluations and it is likely that not every patient will have data at every time point.

10. Review of study results

Analysis of the primary endpoint will be independently reviewed by a member of the Data Analysis team who was not involved in the analysis of the final study data. No additional analysis checks will be carried out.

Study results will be presented to investigators at a meeting to be planned after completion of the data analysis and before the study report is prepared.

11. Pharmacovigilance reporting

11.1. Definitions

11.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The definition of an AE includes worsening of a pre-existing medical condition.

An adverse drug reaction (ADR) is an AE that is considered related to the medicinal product.

11.1.2. Serious Adverse Events

A serious adverse event (SAE) is any AE as defined above that:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other significant medical hazard

A hospitalisation meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

“Other significant medical hazards” refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions,

and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

A serious adverse drug reaction (SADR) is an SAE that is considered related to the medicinal product.

11.2. Reporting Procedures for Adverse Events

All AEs considered related to lurasidone and therefore classified as an adverse drug reaction (ADR) shall be reported by the Principal Investigator at each centre within 24 hours of discovery or notification. In the UK and the Netherlands, ADRs should be reported to vigilance@sunovion.eu and in Switzerland ADRs should be reported to vigilance@medius.ch and safety.eu@sunovion.com. Initial AE information and all follow-up information must be recorded on the AE form and emailed to vigilance@sunovion.eu (UK and Netherlands) or vigilance@medius.ch and safety.eu@sunovion.com (Switzerland). Investigators may be requested to provide follow-up information concerning adverse events, including an evaluation of causality and seriousness.

ADRs for non-Study Sponsor products should be notified by the Principal Investigator at each centre to the appropriate Marketing Authorisation Holder (MAH) and/or to the relevant Regulatory Authority.

11.3. Pregnancy reporting

All pregnancies occurring in female patients while taking lurasidone, and all pregnancies occurring in female partners of male patients taking lurasidone should be reported to vigilance@sunovion.eu (UK and Netherlands) or vigilance@medius.ch and safety.eu@sunovion.com (Switzerland) by the Principal Investigator at each centre within 24 hours of discovery or notification. Initial pregnancy reporting information and all follow-up information must be recorded on the pregnancy reporting form and faxed to vigilance@sunovion.eu (UK and Netherlands) or vigilance@medius.ch and safety.eu@sunovion.com (Switzerland). Investigators may be requested to provide follow-up information concerning pregnancy, including any follow on adverse events.

12. Protection of human subjects

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy, and consistent with the ethical principles of the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) and the requirements of the General Data Protection Regulation (GDPR; https://www.eugdpr.org/the-regulation.html). This study has been designed to minimise the data collected to that which is required for the planned analyses. The data collected will not include any direct identifiers. Data will be transferred to, and held securely by, pH Associates at their offices within the UK during the conduct of this study. The data will not be used for any purpose other than the study described in this protocol.

As the study only involves the collection of data from patients' medical records, there is no additional risk to participants. Patients will have no direct involvement in the study with the exception of providing their informed consent for data to be collected from their medical records.

12.1. Ethical and regulatory approvals

This study is an observational study of routine practice involving the collection of data from patients' medical records. There will be no direct patient involvement with the exception of providing their informed consent for data collection; no changes to patient management and no additional visits are required for the study.

Approval from an independent ethics committee (IEC) or institutional review board (IRB) will be sought in each participating country, according to local requirements. Where required, approval to conduct the study and for release of pseudonymised data for analysis and reporting will also be sought in each participating centre.

12.2. Ethical issues

A patient information sheet will be provided to patients (and/or their carers) identified as being eligible for study participation by the direct care team, explaining the data collection from medical records. Only patients providing written informed consent will be included in the study and no data collection will take place until written informed consent has been

provided (except for deceased patients whose data will be collected by members of the direct care team to preserve patient confidentiality).

No personally identifiable information on any participant will be collected or removed from the study centres participating in the study in order to preserve patient confidentiality.

12.3. Participant privacy

The Data Controller for this study is Sunovion pharmaceuticals Ltd. Data will be collected in pseudonymised format and no personally identifiable information on any participant will be collected or removed from the medical centres participating in the study in order to preserve patient confidentiality. Patients will be assigned a study-specific unique patient identification number which will be referenced in a study log. This patient log will not leave the participating study centre location and will be the responsibility of the principal investigator at that study centre. Pseudonymised participant data will be processed for the purposes of the research study described in this protocol and will be shared with Angelini and Sunovion within the European Economic Area (EAA) and Sunovion based outside the EEA for the purposes of this research study. Sunovion and it's affiliates located outside of the EEA will maintain pseudonymised data in accordance with the recognised EU Model Clause Agreement to safeguard participant anonymity. Participant data will be retained for a period of three years after the end of the study unless a participant withdraws their consent and requests that their data is deleted. Participants will be advised of their right to raise any concerns or complaints related to this research study with the Information Commissioner's Office (https://ico.org.uk/for-organisations/guide-to-the-general-data-protection-regulation-gdpr/individual-rights).

13. Administrative and legal obligations

13.1. Study Amendments and Study Termination

Amendments must be made only by prior agreement between the Study Sponsor, the Study Management Company and the Chief Investigator. The IEC or IRB must be informed of all amendments and give approval for substantial amendments. The Chief Investigator must send a copy of the approval letter from the IEC/IRB to the Study Sponsor.

The Study Management Company, Study Sponsor and the Chief investigator reserve the right to terminate participation in the study according to the study contract. The Study Management Company will notify the IEC/IRB in writing of the study's completion or early termination and send a copy of the notification to the Study Sponsor and the Chief Investigator.

13.2. Study Documentation and Archive

Consistent with ENCePP/ISPE/GDPR guidance, the study documents and data will be archived securely by pH Associates in the UK on behalf of the study sponsor for a period of three years after the end of the study (defined as the date of the final signed Study Report). After this time, with Study Sponsor approval, they will be securely destroyed and the destruction documented. The duration of archiving of study data will ensure that any queries arising from peer review of any ensuing publications can be addressed by reference to the source data if required.

Pseudonymised Data relating to adverse events are to be archived outside of the EU by Sunovion. Sunvion will archive data in accordance with the requirements of the GDPR (https://www.eugdpr.org/the-regulation.html).

14. Communication of study results

The study will be reported according to the requirements of STROBE (Strengthening the reporting of observational studies in epidemiology) as specified in the appropriate checklist for the study design (http://www.strobe-statement.org/index.php?id=available-checklists).

Authorship of any publications arising from the study will follow the guidelines proposed by the International Committee of Medical Journal Editors (2015) (http://www.icmje.org/icmje-recommendations.pdf). All authors will meet the criteria for authorship, and all people who meet the criteria will be authors and all authors will agree to be accountable for the study. Potential conflicts of interest will be disclosed. All authors will have:

(1) made substantial contributions to conception or design or acquisition of data, or analysis and interpretation of data; AND

(2) participated in drafting the publication or revising it critically for important intellectual content; AND

(3) approved the final version to be published.

Each author will have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group will not justify authorship.

15. Study support

The study is sponsored by Sunovion Pharmaceuticals Ltd, the manufacturer of lurasidone. The Study Sponsor has commissioned pH associates to develop materials for and coordinate the conduct of the study, including protocol development, ethical and local approval, data collection, analysis and presentation of the results.

pH Associates is an independent consultancy specialising in the evaluation of healthcare services and interventions in the NHS through observational research, with a focus on the design and implementation of 'Real World Data' projects in order to understand current healthcare practices.

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Annex 1

Dataset to be collected according to study time points and permitted windows, as defined in Section 0.

Variables	Study time points			
	Pre-index observation period	**Baseline (closest within 3 months prior to index date)**	**Index date**	**Post-index observation period**
Date of schizophrenia diagnosis (DD/MM/YYYY)	✓			
Date of initiation of lurasidone (Index date)			✓	
Date of birth (MM/YYYY)	✓			
M/F	✓			
Height (cm), date of measurement		✓		
Weight (Kg), date of measurement		✓		✓
BMI, date of measurement		✓		
Ethnicity	✓			
History of alcohol use (Y/N)	✓			
History of drug abuse (Y/N)	✓			
Smoking status (Y/N) at baseline	✓			
Subtype of schizophrenia (paranoid, disorganized, catatonic, undifferentiated, residual, schizoaffective disorder or other specify)	✓			
Names of all prior anti-psychotic treatments and other therapies (cognitive behavioural therapy, compliance therapy, individual supportive therapy) for schizophrenia	✓			

Variables	Study time points			
	Pre-index observation period	**Baseline (closest within 3 months prior to index date)**	**Index date**	**Post-index observation period**
Dates of initiation of each prior anti-psychotic treatment and other therapies for schizophrenia before index date (DD/MM/YYYY)	✓			
Reason for initiating each prior anti-psychotic treatment or other therapy for schizophrenia before index date	✓			
Names of anti-psychotic treatments and other therapies (cognitive behavioural therapy, compliance therapy, individual supportive therapy) for schizophrenia following initiation of lurasidone (post-index period)				✓
Dates of initiation of each anti-psychotic treatment and other therapies for schizophrenia following the initiation of lurasidone (DD/MM/YYYY)				✓
Reason for initiating each anti-psychotic treatment or other therapy for schizophrenia following the initiation of lurasidone				✓
PANSS total score at baseline		✓		
CGI severity score at baseline		✓		
MADRS total score at baseline		✓		
Related Comorbidities • major depressive disorder • substance abuse		✓		

Variables	Study time points			
	Pre-index observation period	**Baseline (closest within 3 months prior to index date)**	**Index date**	**Post-index observation period**
• hypertension • hyperlipidemia • diabetes • chronic obstructive pulmonary disease • Anxiety				
Blood glucose (mg/dl)		✓		✓
Serum lipids (Total cholesterol, LDL, HDL, triglycerides)		✓		✓
Liver function test results (Albumin, ALT, ALP, AST, GGT)		✓		✓
Reason for initiation of lurasidone			✓	
Total daily dose of lurasidone at initiation			✓	
Dosing regimen of lurasidone at initiation (e.g. once daily, twice daily etc.)			✓	
Stop date of each dose of lurasidone throughout the observation period (DD/MM/YYYY)				✓
Date of initiation of each subsequent new dose of lurasidone (DD/MM/YYYY)				✓
Total daily dose of each subsequent new dose lurasidone				✓
Time of day dose of lurasidone is taken (MM:HH)			✓	✓

Variables	Study time points			
	Pre-index observation period	**Baseline (closest within 3 months prior to index date)**	**Index date**	**Post-index observation period**
Lurasidone commonly taken with a meal (yes/no/not recorded)			✓	✓
Reason for dose change/discontinuation of lurasidone				✓
Dates of first relapse of schizophrenia, as documented in the medical records.				✓
Dates of subsequent relapses of schizophrenia				✓
Body weight (Kg) and date of measurement (DD/MM/YYYY)				✓
Blood glucose (mg/dl) and date of measurement (DD/MM/YYYY)				✓
Serum lipids (Total cholesterol, LDL, HDL, triglycerides) and date of measurement (DD/MM/YYYY)				✓
Liver function test results (Albumin, ALT, ALP, AST, GGT) and date of measurement (DD/MM/YYYY)				✓
Name and date of adverse event judged to be related to the use of lurasidone (DD/MM/YYYY)			✓	✓
Date of hospital admission for a schizophrenia related event (DD/MM/YYYY)				✓

Variables	Study time points			
	Pre-index observation period	**Baseline (closest within 3 months prior to index date)**	**Index date**	**Post-index observation period**
Reason for hospital admission				✓
Date of discharge from hospital for a schizophrenia related event (DD/MM/YYYY)				✓
Speciality department for hospital admission				✓
Elective/non-elective admission to hospital				✓
Date of admission to emergency department for a schizophrenia related event (DD/MM/YYYY)				✓
Date of discharge from emergency department for a schizophrenia related event (DD/MM/YYYY)				✓
Date of schizophrenia outpatient visits (DD/MM/YYYY)				✓