Prospective Observational Study Protocol F1D-MC-B034 Observational Study Description F1D-MC-B034(c) Post-Injection Syndrome in Patients with Schizophrenia Receiving Olanzapine Long-Acting Injection

Confidential Information

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Post-Injection Syndrome in Patients with Schizophrenia Receiving Olanzapine Long-Acting Injection

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Post-Injection Syndrome in Patients with Schizophrenia Receiving Olanzapine Long-Acting Injection

Summary of the Study

Study F1D-MC-B034 (B034) is a noninterventional prospective study designed to assess the incidence of Post-Injection Syndrome events in patients treated with olanzapine Long-Acting Injection (olanzapine LAI). This study is planned to be conducted in multiple countries where olanzapine LAI is marketed. For Study B034, a Post-Injection Syndrome event is defined as an event reported in temporal association with an injection of olanzapine LAI that presents with signs and symptoms consistent with olanzapine overdose (post injection). Most patients have developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety, and other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension, or possible convulsion.

The investigator will record on the data capture form all adverse events (AEs) that occur within 24 hours following an injection and will provide a clinical opinion as to whether the patient has experienced a potential Post-Injection Syndrome event. An Adjudication Committee will review all these cases and will determine whether a case of interest is excluded from further categorization.

The study will characterize the clinical presentation and outcomes of Post-Injection Syndrome events, as well as seek to identify potential risk factors associated with their occurrence.

Approximately 5000 patients will enter this multicenter study to achieve 92,500 injections that will be included in event incidence calculations.

1. Introduction

Olanzapine Long-Acting Injection (olanzapine LAI) is a sustained-release intramuscular (IM) dosage formulation of olanzapine, and has been studied in clinical trials since 2000. As of 31 January 2009, over 59,482 injections have been administered to 2,054 patients. As of this cutoff date, 39 Post-Injection syndrome (also known as Post Injection Delirium Sedation Syndrome [PDSS]) events have been reported in 38 patients. Clinical presentation was consistent with many symptoms of oral olanzapine overdose; most patients experiencing a Post-Injection Syndrome event have developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety, and other cognitive impairment). Other symptoms seen include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension, or possible convulsion. No respiratory depression or clinically significant decreases in blood pressure were noted. Further information on the presentation of these events as well as the possible mechanism for the events can be referenced in publications by Detke et al (2010) and McDonnell et al (2010).

The mechanism of these events is probably related to higher solubility of olanzapine LAI in blood than in muscle. Increased contact with a substantial volume of blood could occur in several ways: partial injection into the vasculature, vessel injury associated with the IM injection, such as a nick or puncture of the blood vessel, or substantial bleeding at the injection site. With any of these, there could be a "rapid release" of a portion of the olanzapine LAI dose. Higher than expected systemic olanzapine concentrations have been observed in patients experiencing a Post-Injection Syndrome event.

As of 31 January 2009, the incidence of Post-Injection syndrome events in patients treated with olanzapine LAI in clinical trials is approximately 0.07% of injections (1.85% of patients). In most cases, initial signs and symptoms related to this event have appeared within 1 hour following injection, and in all cases full recovery was reported to have occurred within 24 to 72 hours after injection. Events occurred rarely (<1 in 1000 injections) between 1 and 3 hours, and very rarely (<1 in 10,000 injections) after 3 hours.

This observational trial is designed to estimate the incidence of Post-Injection Syndrome events in "real world" clinical practice, as well as better characterize the clinical presentation and outcomes. This study will also seek to identify potential risk factors associated with Post-Injection Syndrome events.

2. Objectives

2.1. Primary Objective

The primary objective of this study is to:

- estimate the incidence per injection and per patient of Post-Injection Syndrome events in schizophrenia patients receiving olanzapine LAI.

2.2. Secondary Objectives

The secondary objectives of this study are to:

- further characterize the clinical presentation, including the outcomes of Post-Injection Syndrome events
- identify potential risk factors associated with Post-Injection Syndrome events
- characterize hospitalization at baseline (previous 6- or 12-month) and postbaseline

3. Methods

3.1. Summary of Study Design

Study F1D-MC-B034 is a prospective observational study to assess the incidence of Post-Injection Syndrome events in schizophrenia patients receiving olanzapine LAI.

Observational studies represent noninterventional research; therefore, these studies do not involve randomization of patients to particular comparator arms or therapies. The term "noninterventional" means that the healthcare provider's decisions regarding the proper treatment and care of the patient are made in the course of normal clinical practice. Patients enrolled in this study are enrolling for the collection of their data on observations made during normal clinical practice.

The study is planned to be conducted at sites in multiple countries where olanzapine LAI is marketed. Patient treatment, dosing, and AE management are at the discretion of the investigator. For this study, based upon the investigator's clinical judgment, a Post-Injection Syndrome event is defined as an event or events reported in temporal association with an injection of olanzapine LAI that presents with signs and symptoms consistent with olanzapine overdose. An Adjudication Committee will review all serious adverse events in this study to determine whether a case of interest is a confirmed Post-Injection Syndrome event based upon the committee's predefined decision algorithm (see Section 3.3.3).

Approximately 5000 patients will enter this study, to achieve an estimated number of 92,500 injections. Additional patients may be needed to achieve the desired number of injections.

Study enrollment will occur when the patient provides consent to release medical information. Data collection point (DCP) 1 then occurs at the first olanzapine LAI injection after the patient provides consent. At DCP 1, the investigator will record baseline information. Patients do not need to be olanzapine LAI naive to participate in this study. The frequency of DCPs will depend on the frequency that the patient is receiving olanzapine LAI injections. Data collected at every DCP (i.e., every injection of olanzapine LAI) are summarized in Attachment B034.1.

More detailed data will be recorded if the patient has a potential Post-Injection Syndrome event, if applicable and if possible.

3.2. Study Population

Eligible patients will include adult patients with schizophrenia whose physician has decided to treat with olanzapine LAI.

3.2.1. Selection Criteria

Patients are eligible to be included in the study if they meet all of the following criteria:

- They are male or female patients, at least 18 years of age who have been diagnosed with schizophrenia.

- They are willing to participate in the study and have signed a consent form to release medical information.
- They do **not** meet **any** of the following criteria:
    - They are investigator site personnel directly affiliated with the study and/or their immediate family. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
    - They are Lilly employees.
    - They are unwilling to provide written consent to release medical information or other required forms to participate in the study.

3.2.2. Patient Groups

There are no assigned treatment groups for this study.

3.2.3. Patient Discontinuation from Study

Possible reasons for discontinuation of a patient from observation include death, AE, patient decision, investigator decision, lost to follow-up, and sponsor decision. All information related to a death (regardless of relationship to the study or study medication) will be collected.

3.3. Study Therapies

All patients will receive commercially-available olanzapine LAI in accordance with their physician's standard of care.

Treatment is solely at the discretion of the physician and the patient. Treatment for schizophrenia will be prescribed in the usual standard of care and will not be provided by the study sponsor. Participation in the study will in no way influence payment or reimbursement for any treatment received by patients during the study.

It is recommended that investigators follow the country- or region-specific labeling (e.g., Summary of Product Characteristics).

3.3.1. Assessment of Treatment Outcomes

Study enrollment will occur when the patient provides consent to release medical information. DCP 1 will occur at the first administration of olanzapine LAI after consent. The investigator will record all baseline information, including demographics, year of initial diagnosis of schizophrenia, all prior depot antipsychotic medication use, history of psychiatric drug use, and previous psychiatric hospitalization information.

The frequency of DCPs will depend on the frequency that the patient is receiving olanzapine LAI. Every administration of olanzapine LAI will be considered a DCP. If the patient is seen by study staff, but does not receive olanzapine LAI, this is not to be reported as a new DCP in the electronic data capture system. Any relevant observations made by the investigator or reported to the investigator are to be recorded on the appropriate data form (electronic case report form).

Data collected at every DCP will include all AEs, all current medications (including over-the-counter), recreational substance use in the past 24 hours (except for nicotine and caffeine use), mental status at the end of the observation period, date and time of injection, size of needle (length and gauge) used for injection, clinical setting of injection administration, dose, collection of the frequency of metabolic monitoring, and psychiatric hospitalization information. The frequency of metabolic monitoring is being collected to assess adherence to label or metabolic guideline recommendations. The actual lab results (if performed) will not be collected. These data collected at every DCP are summarized in Attachment B034.1.

More detailed data are to be recorded if the patient has a potential post-injection syndrome event, if applicable and if possible, such as date/time of event onset and date of event resolution

Attachment B034.1 outlines the data to be collected at each DCP.

3.3.2. Operational Definition of Post-Injection Syndrome Event

A patient should be considered by the investigator to have a potential Post-Injection Syndrome event if, after ruling out oral overdose of any drug, based upon the investigator's clinical judgment, the following two conditions are met:

- The patient presents with signs and symptoms (most commonly sedation and delirium-related AEs) of clinical severity consistent with those reported with an olanzapine overdose, and
- The signs and symptoms are reported in temporal association with an injection of olanzapine LAI.

Most patients who experienced a Post-Injection Syndrome event have developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety, and other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension, or possible convulsion.

Detailed training regarding the signs and symptoms of olanzapine overdose will be provided to the study team and study site staff.

3.3.3. Adjudication Committee Review of Post-Injection Syndrome Events

An Adjudication Committee will review all serious adverse events including cases reported as potential Post-Injection Syndrome events by the study investigator. To provide consistency and to minimize the occurrence of false positive assessments, the committee will utilize predefined criteria when reviewing potential Post-Injection Syndrome events. The determination of whether the reported events meet the predefined Post-Injection Syndrome events criteria will be decided by consensus of the Adjudication Committee. All members of the Adjudication Committee will have experience in assessing and identifying Post-Injection syndrome events. The Adjudication Committee will not include a B034 study investigator as a member.

4. Sample Size and Statistical Methods

4.1. Determination of Sample Size

Based on the patient retention rates of Study HGKB through 30 September 2007, it is anticipated that the approximately 5000 patients to be observed in Study B034 will experience at least 92,500 injections. Based on the estimated incidence by injection (0.072%) as of 15 July 2008, this number of injections will have at least 80% power to show the proportion of injections resulting in a Post-Injection Syndrome event (θ) is less than 0.10%. It is the intent of this study to show the rate of Post-Injection Syndrome events in olanzapine LAI to be less than 0.10%. More patients may need to be enrolled to ensure that at least 92,500 injections are administered.

Assuming a null hypothesis proportion θ to be 0.072%, an exact binomial test with a nominal 0.05 two-sided significance level will have at least 80% power to detect the difference between θ_0 of 0.072% and the alternative proportion of 0.10% when the number of injections is 92,500. In terms of events per patient, assuming a null hypothesis θ_0 to be 1.36% (estimated incidence by patient as of 15 July 2008), this sample size will allow for at least 70% power to detect the difference between θ_0 and the alternative proportion of 2% at the 0.05 two-sided significance level.

4.2. Statistical and Analytical Plans

4.2.1. General Considerations

Statistical analyses will be performed by the sponsor or their designee. The statistical analysis plan created for this study will contain additional details on planned analyses.

4.2.1.1. Study Population

All patients who provide consent to release information and who fulfill the study entry criteria will be included in the analyses. For those patients who are lost to follow-up, or who drop out of the study, the analyses will include all data up to the point of their last data collection. Due to the observational nature of this study, patients who violate the protocol will be included in the analyses.

4.2.1.2. Missing Data

The statistical analysis plan created for this study will address the handling of missing data.

4.2.1.3. Significance Levels

A confidence interval will be two-sided at a 95% level.

4.2.1.4. Adjustments for Covariates

Due to the observational nature of this study, covariate adjustments will be made to control for biases and confounding where appropriate.

4.2.2. Treatment Outcome Analyses

4.2.2.1. Primary Outcome Analysis

Crude incidence of Post-Injection Syndrome events and 95% confidence intervals will be calculated based on the total number of patients enrolled in the study and the total number of injections given in the study period. Post-Injection Syndrome events used in the incidence calculation will be based on adjudicated cases.

4.2.2.2. Secondary Outcome Analyses

Descriptive statistics will be used to describe the study population and characterize the clinical presentation of Post-Injection Syndrome events including outcome.

Adjusted odds ratios and 95% confidence intervals will be calculated using logistic regression to identify risk factors for patients experiencing Post-Injection Syndrome events.

4.2.3. Health Outcome Analysis

Hospitalization at baseline (previous 6- or 12-month) and postbaseline will be tabulated for all enrolled patients. Descriptive statistics will be used to describe the frequency and duration of hospitalization.

4.2.4. Safety Analysis

Adverse event and serious adverse event (SAE) data will be summarized with descriptive statistics.

4.2.5. Subgroup Analyses

Subgroups may be identified and subgroup analyses conducted as deemed appropriate.

4.2.6. Interim Analyses

As this is an observational study, every 6 months AEs and SAEs are reviewed. In addition, the incidence of Post Injection Events are reviewed at least annually. Interim analyses will be conducted if deemed necessary at any time during the study.

5. Safety Evaluations

5.1. Adverse Events

The investigator or other study personnel will record via electronic data entry all adverse events (AEs) they become aware of arising in temporal association with Lilly drug(s) under evaluation as defined in this protocol. Additionally, personnel will record via electronic data entry any change in the condition(s) and/or the occurrence and nature of these AEs.

If an investigator becomes aware of AEs occurring to a subject after the subject's participation in the study has ended, the investigator should report the AEs to the sponsor. These AEs collected will be included in the Pharmacovigilance system of the sponsor.

Additionally, the investigator or other study personnel will record via study-specific SAE form the following safety information for Lilly drugs under evaluation, regardless of whether there is an associated adverse event:

- pregnancy exposures
- breast-feeding exposures
- overdoses
- misuse
- abuse
- medication error
- lack of drug effect
- off-label use
- suspected transmission of infectious agent

Investigators and other study personnel are requested to report adverse reactions in temporal association with Lilly drugs not under evaluation per this protocol or non-Lilly drugs to the appropriate party (for example, regulators or Lilly) as they would in normal practice as required by applicable laws, regulations, and practices. Standard postmarketing practices for reporting AEs to local regulatory bodies should also be followed for any AEs occurring in temporal association with the study drug.

The investigator or other study personnel will report to Lilly or its designee any **nonserious** adverse event arising in temporal association with the Lilly drug(s) under evaluation within 30 days of awareness of the event via a sponsor-approved method.

5.2. Serious Adverse Events

The investigator or other study personnel will report to Lilly or its designee any **serious** adverse event (SAE) arising in temporal association with the Lilly drug(s) under evaluation within 24 hours of awareness of the event via a Sponsor-approved method. Reports issued via telephone

are to be immediately followed with official notification on study-specific SAE forms. An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- or is considered significant by the investigator for any other reason.
- For study purposes, all potential Post-Injection Syndrome events should be reported to Lilly, or its designee, as SAEs utilizing the reporting category of "Other" in case the event does not meet any other SAE criterion. Potential Post-Injection Syndrome events should be reported using the same procedure as all SAEs.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse drug events (ADEs) when, based upon appropriate medical judgment, they may jeopardize the patient.

5.3. Complaint Handling

Lilly collects product complaints on study drugs and drug delivery systems used in medical research studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements. Product complaints will be reported in the same way that any complaints on prescribed products are reported to the manufacturer.

6. Patient Consent to Release Information, Ethical Review, and Regulatory Considerations

6.1. Patient Consent to Release Information

This is an observational research program and does not impose any form of intervention on the investigator. Hence, the assessment and treatment of patients is based solely on the investigator's routine or usual practice in the provision of care to patients with schizophrenia.

As this is an observational study, the patient will provide authorization for the uses and disclosures of their personal health information as described in the study Consent to Release Information. This consent covers the collection and release of data regarding treatment and its outcomes for the entire period of the study. The confidential nature of the patient information will be maintained.

6.2. Ethical Review and Regulatory Considerations

Observational studies will be submitted to ethical review boards (ERBs) for approval whenever required by local law. In addition, regardless of local law, all prospective observational studies will be submitted to at least one ERB per country for review and to confirm that the study is considered noninterventional in that country. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and applicable laws and regulations of the country or countries where the study is being conducted, as appropriate.

7. Record Keeping, Data Reporting, Data Quality Assurance, and Publications

Patient data are to be recorded on simple, unambiguous data forms. Investigators are responsible for the integrity of the data (that is, accuracy, completeness, legibility, and timeliness) reported to Lilly. The investigator is to follow local laws and regulations or institutional practices for document retention. An electronic data capture system will be used in this trial. All data will be collected on a source document (for example, work sheet or patient chart) and will then be entered into the electronic data capture system by the investigator or his/her designee. These case report form data will be encoded and stored electronically on case report forms in a clinical trial database. Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

All information about this observational study and individual patient medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities and as applicable by law. Publications will result from this study, and appropriate dissemination of study data will be planned. However, the data emerging from this study cannot be released without Lilly's prior permission, as the data emerging from this study are the property of the sponsor. Publications will be produced in accordance with Lilly's policies on publications and authorship. The final decision on authorship positioning or any other publication issues will be made by Lilly.

8. References

Cummings JL, Barritt CF, Horan M. 1987. Delusions induced by procaine penicillin: case report and review of the syndrome. Int J Psychiatry Med. 16(2):163-168.

Carmo de Casto Miranda M, Rozenfeld S, Pacheco de Oliveira S. 2004. A systemic review of the non-allergic adverse reactions following benzathine benxylpenicillin injection. J Vasc Br. 3(3):253-260.

Detke HC, McDonnell DP, Brunner E, Zhao F, Sorsaburu S, Stefaniak VJ, Corya SA. Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, I: analysis of cases. *BMC Psychiatry.* 2010;10:43.

Downham TF 2nd, Cawley RA, Salley SO, Dal Santo G. 1978. Systemic toxic reactions to procaine penicillin G. Sex Transm Dis. 5(1):4-9.

[ISMP] Institute for Safe Medication Practices. ISMP medication safety alert. May 29, 2003.

[ISMP] Institute for Safe Medication Practices. ISMP medication safety alert. May 6, 2004.

McDonnell et al: Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, II: investigations of mechanism. *BMC Psychiatry* 2010 10:45.

Sen S, Chini EN, Brown MJ. 2005. Complications after unintentional intra-arterial injection of drugs: risks, outcomes, and management strategies. Mayo Clin Proc. 80(6):783-795.

Attachment 1. Observational Study Description Attachment B034.1. Data Collection Schedule

Table 1 Data Collection Schedule, Observational Study Description F1D-MC-B034

Descriptions of Data*	Baseline	During Therapy	
	Day 1	Every Injection Visit	Injection Visit with Potential Event
Data Collection Point (DCP)[a]	DCP-1 (Date of First Injection: V1)	DCP-2, DCP-3, etc (Date of Injection)	Any DCP that Potential Event Occurs
Informed Consent	X		
Demographics	X		
Height	X		
Weight	X	X	
Medical History Disease Characteristics, Psychiatric History	X		
Consumption Habits During the Study[b]	X	X	
Current Medical Status: Lab Event[f]	X	X	
Previous Therapy (Antipsychotics)	X		
Olanzapine Long-Acting Injection	X	X	
Mental Status Assessment at the End of the Observation Period	X	X	
Pre-existing Conditions, Adverse Events[c]	X	X	X[d]
Concomitant Therapy[e]	X	X	X
Current Medical Status: Post-Injection Syndrome Event			X
Study Adverse Events: 24 Hours Post Injection			X
Psychiatric Hospitalization Information[g]	X	X	X
Subject Summary	X	X	

Abbreviations: DCP=Data Collection Point

[a] For purposes of electronic database collection only, a Data Collection Point (DCP) has the same meaning as a Visit within the electronic data capture system.

[b] Current Consumption Habits are those recreational drugs that have been used or consumed within the previous 24 hours prior to the injection of olanzapine LAI. These substances include amphetamine/methamphetamine, barbiturate, cannabinoid, cocaine, hallucinogen, opiate, phencyclidine, and alcohol.

[c] For Adverse Events occurring between Data Collection Points (DCPs), collect the event term, the start date, the stop date (if applicable), the severity, and the seriousness.

[d] For Adverse Events occurring within 24 hours following an injection of olanzapine LAI, collect the start time of the event, event term, the start date, the stop date, the severity, and the seriousness. Within the source documentation, collect the date and time that the post-injection adverse event was resolved.

[e] For Concomitant Therapy taken between Data Collection Points (DCPs), collect the treatment name, start date, the total daily dose, and the stop date (if applicable). For any Concomitant Therapy taken or prescribed specifically to treat post-injection adverse events, within the source documentation, collect the treatment name, start date and start time, the total daily dose, and the stop date and stop time (if applicable).

[f] As there are no labs collected in this study, the Current Medical Status: Lab event form will collect the status of metabolic monitoring, the frequency of metabolic monitoring is being collected to assess adherence to label or metabolic guideline recommendations. The actual lab results (if performed) are not collected.

[g] Psychiatric Hospitalization is defined as at least one overnight stay for psychiatric purposes.

Attachment 2. Protocol Amendment F1D-MC-B034(c) Post-Injection Syndrome in Patients with Schizophrenia Receiving Olanzapine Long-Acting Injection

Overview

Protocol F1D-MC-B034(c) Observational Study Description F1D-MC-B034(c) Post-Injection Syndrome in Patients with Schizophrenia Receiving Olanzapine Long-Acting Injection has been amended. The new protocol is indicated by amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Correction of an inadvertent omission of a secondary objective. The global health outcome objective of characterizing hospitalization at baseline (previous 6- or 12-month) and postbaseline has now been added to Section 2.2. This measurement and its analysis were already described in Section 3.3.1 (Assesment of Treatment Outcomes), Section 4.2.3 (Health Outcome Analysis), and Attachment 1 (Data Collection Schedule).
- Correction to wording in Section 3.2.3 (Patient Discontinuation from Study). The word "Criteria" had inadvertently been used when what was intended was "Possible reasons." The items listed do not represent criteria for automatic discontinuation but instead represent possible reasons that a patient might discontinue the study.
- Addition of updated required protocol template title page and text in Section 5.1 (Adverse Events) and Section 5.2 (Serious Adverse Events), including new text that states that investigators and other study personnel are requested to report adverse reactions associated with Lilly and non-Lilly drugs to Lilly as well as local regulatory bodies, as they would in normal practice as required by applicable laws, regulations, and practices.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- further characterize the clinical presentation, including the outcomes of Post-Injection Syndrome events
- identify potential risk factors associated with Post-Injection Syndrome events
- characterize hospitalization at baseline (previous 6- or 12-month) and postbaseline

3.2.3 Patient Discontinuation from Study

~~Criteria~~ Possible reasons for discontinuation of a patient from observation include death, AE, patient decision, investigator decision, lost to follow-up, and sponsor decision. All information related to a death (regardless of relationship to the study or study medication) will be collected.

3.3.1 Assessment of Treatment Outcomes

The frequency of DCPs will depend on the frequency that the patient is receiving olanzapine LAI. Every administration of olanzapine LAI will be considered a DCP. If the patient is seen by study staff, but does not receive olanzapine LAI, this is not to be reported as a new DCP in the electronic data capture system. Any relevant observations made by the investigator or reported to the investigator are to be recorded on the appropriate data form (electronic case report form).

5.1 Adverse Events

~~During the study,~~ The investigator or other ~~site~~ study personnel will record via ~~data form~~ electronic data entry ~~any~~ all adverse events (AEs) they become aware of arising in temporal association with ~~the~~ Lilly drug(s) under ~~study~~ evaluation as defined in this protocol. ~~and~~ Additionally, personnel will record via electronic data entry any change in the condition(s) and/or the occurrence and nature of these AEs.

If an investigator becomes aware of AEs occurring to a subject after the subject's participation in the study has ended, the investigator should report the AEs to the sponsor. These AEs collected will be included in the Pharmacovigilance system of the sponsor

Additionally, the investigator or other study personnel will record via study-specific SAE form the following safety information for Lilly drugs under evaluation, regardless of whether there is an associated adverse event:

- pregnancy exposures
- breast-feeding exposures
- overdoses
- misuse
- abuse
- medication error
- lack of drug effect
- off-label use
- suspected transmission of infectious agent

Investigators and other study personnel are requested to report adverse reactions in temporal association with Lilly drugs not under evaluation per this protocol or non-Lilly drugs to the appropriate party (for example, regulators or Lilly) as they would in normal practice as required by applicable laws, regulations, and practices. Standard postmarketing practices for reporting AEs to local regulatory bodies should also be followed for any AEs occurring in temporal association with the study drug.

The investigator or other study personnel will report to Lilly or its designee any **nonserious** adverse event arising in temporal association with the Lilly drug(s) under evaluation within 30 days of awareness of the event via a sponsor-approved method.

5.2 Serious Adverse Events

The investigator or other study site personnel will ~~notify~~ report to Lilly or its designee ~~of~~ any **serious** adverse event (SAE) arising in temporal association with the Lilly drug(s) under evaluation within 24 hours of ~~investigator~~ awareness of the event via a Sponsor-approved method. ~~Alerts~~ Reports issued via telephone are to be immediately followed with official notification on study-specific SAE forms. An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- or is considered significant by the investigator for any other reason.
- For study purposes, all potential Post-Injection Syndrome events should be reported to Lilly, or its designee, as SAEs utilizing the reporting category of "Other" in case the

event does not meet any other SAE criterion. Potential Post-Injection Syndrome events should be reported using the same procedure as all SAEs.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse drug events (ADEs) when, based upon appropriate medical judgment, they may jeopardize the patient ~~and may require medical or surgical intervention to prevent one of the outcomes listed in this definition~~.

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