INTRODUCTION

How Do Disease Progression and Disease Modification Differ?

- Disease progression: worsening of a disease in terms of symptom severity, underlying pathology, or outcome
- Disease modification: alteration of the underlying disease pathophysiology that results in a beneficial outcome

What Are Delayed-Start Study Designs?

- Delayed-start study designs are used to distinguish between a treatment’s effect on symptomatic improvement and potential disease modification
  - They are primarily used to evaluate treatments for slowly progressing and debilitating diseases, such as Parkinson’s disease and Alzheimer’s disease
- In general, delayed-start study designs have two phases:
  - Phase 1: patients are randomly assigned to receive active or placebo; they are then followed for an extended period of time to track disease progression and observe the effects of treatment on symptoms
  - Phase 2: all patients receive active treatment, and data obtained during this phase are used to evaluate the disease-modifying effects of active treatment

DISEASE RECOVERY EVALUATION AND MODIFICATION (DREAM) STUDY

Objective

- To examine whether an LAI with a 1-month and 3-month injection schedule can slow disease progression and possibly modify the course of schizophrenia compared to oral antipsychotics (OAs) in patients with recent-onset schizophrenia or schizophreniform disorder by tracking changes in cognition, functioning, and ICM volume and by tracking treatment failure
- Disease modification is based on a totality-of-evidence approach that evaluates the course and pathophysiology of the illness with measures of symptoms, functioning, and biological changes

Study Design

- DREAM (NCT02431702) is a prospective, matched-control, double-blind, randomized, open-label, flexible-dose study in subjects with recent-onset schizophrenia or schizophreniform disorder to compare disease progression and disease modification following treatment with once-monthly and once-every-3-months LAI or OAs
- Overview of study design (Figure 2): Patients with a Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5) diagnosis of schizophrenia or schizophreniform disorder and first psychotic episode within 2 years are eligible

Figure 2. Schematic of DREAM study.

Assessments

- Overall primary end point: time to first treatment failure in Part 2, comparing LAI and OA. Treatment failure was defined as:
  - Psychiatric hospitalization due to worsening symptoms (including emergency department visits ≥23 hours)
  - Deliberate self-injury, suicidal ideation or behavior, homicidal ideation, or violent behavioral dysfunction
  - Increase in the level of psychiatric services in order to prevent imminent psychiatric hospitalization
  - Non arrest/incarceration
  - Discontinuation of antipsychotic treatment due to inadequate efficacy or a safety/tolerability issue
  - Supplementation with another antipsychotic drug due to inadequate efficacy (including OA supplementation to LAI treatment)
  - Changes in cognition via MCCB, patient functioning (assessed with the Personal and Social Performance scale), and ICM volume (via magnetic resonance imaging) will all be assessed as measures of disease progression (in Parts 2 and 3) and modification (in Part 3)
- A sample size of 275 subjects is planned (~50% with ICM assessment)

- Hypothetical outcomes of the DREAM study are shown schematically in Figure 3 using an MCB composite score
- In Part 2, we expect that patients randomly assigned to OAs will experience a greater magnitude of disease progression than those receiving LAI.
- In Part 3, if LAI has disease-modifying effects, the two LAI groups (immediate start and delayed start) will have similar slopes. The “failure to catch up” concept is suggested by the parallel lines and indicates disease-modifying effect (Figure 3A).
- If LAI does not have disease-modifying effects, there will be a significant decrease in the size of δ, versus the start of Part 3 (δ delayed-treatment benefit is measured by the size of δ (Figure 3B))

Figure 3. Hypothetical outcomes of DREAM: (A) treatment effect on disease progression and modification and (B) delayed-start treatment effect.

Key Components of DREAM Study

- Randomized, multicenter study comparing the impact of oral and LAI antipsychotics on:
  - Treatment failure in recent-onset schizophrenia
  - Functional outcomes in recent-onset schizophrenia
  - Cognitive performance in recent-onset schizophrenia
- Blinded ratings of ICM volume in recent-onset schizophrenia
- Randomized matched controls
- Prospective run-in with static and dynamic prognostic factors
- 2-month run-in period will also help to identify subjects who have a propensity to discontinue
- Randomized delayed-start
- Verification and quantification of delayed-start effect
- Disease modification as a clinical judgment based on the totality of evidence (ie, effect on disease progression [δ], lead effect after early start [δ], delayed-start effect [δ], cumulative effect on progression [δ], and biomarker effects)

DISCUSSION

- Key features of the DREAM study include:
  - A flexible-dose run-in period in (1) collect demographic and baseline patient characteristics needed for the matched-control analysis and (2) identify subjects likely to discontinue the study, thereby reducing dropout rates during Parts 2 and 3
  - A randomized, matched-control of patients for a double-blind randomized delayed-start design to evaluate disease modification effects
  - DREAM, to the best of our knowledge, will provide the largest dataset of ICM images acquired during treatment in a population of patients with recent-onset schizophrenia
  - The study’s results may provide important insights into disease progression and potential disease modification in recent-onset schizophrenia and into the comparative effectiveness of LAIs and OAs used to treat this disorder

REFERENCES


Acknowledgments

The authors thank Matthew guywacz, PhD, and Lyn Brown, PhD, for their writing and editorial assistance.

Disclosures

Janssen Scientific Affairs, LLC (JSA) is an employee of Janssen Scientific Affairs, LLC, and Johnson & Johnson stockholders. P. Turkus is an employee of Janssen Research & Development, LLC, and a Johnson & Johnson stockholder.
How Do Disease Progression and Disease Modification Differ?

- Disease progression: worsening of a disease in terms of symptom severity, underlying pathology, or outcome
- Disease modification: alteration of the underlying disease pathophysiology that results in a beneficial outcome

The term “disease progression” is most commonly used for chronic and incurable diseases where the stage of the disease is an important determinant of therapy and prognosis.

What Are Delayed-Start Study Designs?

- Delayed-start studies are used to distinguish between a treatment’s effect on symptomatic improvement and potential disease modification.
  - They are primarily used to evaluate treatments for slowly progressing and debilitating diseases, such as Parkinson’s disease and Alzheimer’s disease.
- In general, delayed-start studies have two phases:
  - Phase 1: Patients are randomly assigned to receive active or placebo. They are then followed up for an extended period of time to track disease progression and observe the effects of treatment on symptoms.
  - Phase 2: All patients receive active treatment, and data obtained during this phase are used to evaluate the disease-modifying effects of active treatment.
- Deep knowledge of the disease under study and careful selection and implementation of statistical methods are needed for a successful delayed-start study design.
- One of the major drawbacks of a delayed-start study design is that a long treatment period is needed to demonstrate the intervention’s effect on disease progression.
- Consequentially, a high percentage of subjects may drop out before entering into the delayed-start period. This invalidates existing analytic approaches for demonstrating disease modification.

Why Focus on the Early Course of Schizophrenia?

- Evidence from a variety of studies suggests that early-stage schizophrenia is most amenable to better outcomes.
  - When first-episode schizophrenia is adequately treated, psychotic symptoms are usually well managed and patients functionally return to a premorbid state.
  - Better treatment response is usually observed in first-episode patients or early in the course of illness. With subsequent relapses, recovery tends to be less complete.
  - Cognitive impairment and dysregulated developmental trajectory of frontal lobe myelination are enduring components of schizophrenia. However, early intervention may increase the effectiveness of treatment with antipsychotic medication, and it may mitigate biological changes that are characteristic of chronic or refractory disease states.
- Recent studies11 in patients with first-episode schizophrenia have shown that formulation impacts efficacy, with greater improvements observed with a long-acting injectable (LAI) antipsychotic versus an oral antipsychotic in terms of:
  - Reducing time to relapse (Figure 1)
  - Improving cognition scores (as assessed by the MATRICS Consensus Cognitive Battery [MCCB]) overall composite score, (P = 0.09) and in the areas of working memory (P = 0.08) and verbal learning (P = 0.07).
  - Increasing intracortical myelin (ICM).12

**Figure 1. Kaplan-Meier curve of time to relapse.**

**DISEASE RECOVERY EVALUATION AND MODIFICATION (DREAM) STUDY**

**Objective**

- To examine whether an LAI with a 1-month and 3-month injection schedule can slow disease progression and possibly modify the course of schizophrenia compared to oral antipsychotics (OAs) in patients with recent-onset schizophrenia or schizoaffective disorder.
- To track changes in cognition, functioning, and ICM volume and by tracking treatment failure.
- Disease modification is based on a totality-of-evidence approach that evaluates the course and pathophysiology of the illness with measures of symptoms, functioning, and biological changes.

**Study Design**

- **DREAM (NCT02431762)** is a prospective, matched-control, double-randomized, open-label, flexible-dose study in subjects with recent-onset schizophrenia or schizoaffective disorder to compare disease progression and disease modification during treatment with once-monthly and once-every-3-months (LAI or OAs).
- **Overview of study design** (Figure 2)
  - Patients with a DREaM (Diagnostic and Statistical Manual of Mental Disorders [5th ed.; DSM-5]) diagnosis of schizophrenia or schizoaffective disorder and first psychotic episode within 2 years are eligible.

**Figure 2. Schematic of DREAM study.**

**Assessments**

- **Overall primary end point:** time to first treatment failure in Part 2, comparing LAI and OA. Treatment failure was defined as:
  - Psychiatric hospitalization due to worsening symptoms (including emergency department visits ≥33 hours)
  - Deliberate self-injury, suicidal ideation or behavior, homicidal ideation, or violent behavior that is clearly dysfunctional
  - Increase in the level of psychiatric services in order to prevent imminent psychiatric hospitalization
  - Need for increased psychiatric services in order to prevent imminent psychiatric hospitalization
  - Discontinuation of antipsychotic treatment due to inadequate efficacy or a safety/tolerability issue
  - Supplementation with another antipsychotic due to inadequate efficacy (including OA supplementation to LAI treatment)
  - Changes in cognition via MCCB, patient functioning (assessed with the Personal and Social Performance scale), and ICM volume (via magnetic resonance imaging) will all be assessed as measures of disease progression (in Parts 2 and 3) and modification (in Part 3).
- A sample size of 275 subjects is planned (∼50% with ICM assessment).
- Hypothetical outcomes of the DREAM study are shown schematically in Figure 3 using an MCCB composite score.
- In Part 2, we expect that patients randomly assigned to OAs will experience a greater magnitude of disease progression than those receiving LAI.
- In Part 3, if LAI has disease-modifying effects, the two LAI groups (immediate start and delayed start) will have similar slopes. This “failure to catch up” concept is suggested by the parallel lines and indicates disease-modifying effect (Figure 3A).
- If LAI does not have disease-modifying effects, there will be a significant decrease in the size of δ, versus the start of Part 3 (δ delayed-start treatment benefit is measured by the size of δ) (Figure 3B).

**REFERENCES**


Acknowledgments

The authors thank Matthew Grzywacz, PhD, and Lynn Brown, PhD, for their writing and editorial assistance.

Disclosures

I. Turkov is a consultant to Janssen Scientific Affairs, LLC, and Johnson & Johnson stockholders. I. Turkov is an employee of Janssen Research & Development, LLC, and a Johnson & Johnson stockholder.

**Supporting Information**


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**INTRODUCTION**

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- Disease progression: worsening of a disease in terms of symptom severity, underlying pathology, or outcome
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**What Are Delayed-Start Study Designs?**

- Delayed-start study designs are used to distinguish between a treatment's effect on symptomatic improvement and potential disease modification:
  - They are primarily used to evaluate treatments for slowly progressing and debilitating diseases, such as Parkinson's disease and Alzheimer's disease.
  - In general, delayed-start studies have two phases:
    - Phase 1: patients are randomly assigned to receive active or placebo. They are then followed up for an extended period of time to track disease progression and observe the effects of treatment on symptoms.
    - Phase 2: all patients receive active treatment, and data obtained during this phase are used to evaluate the disease-modifying effects of active treatment.

**Why Focus on the Early Course of Schizophrenia?**

- Evidence from a variety of studies suggests that early-stage schizophrenia is most amenable to better outcomes:
  - When first-onset schizophrenia is adequately treated, psychotic symptoms are usually well managed and patient functioning typically returns to a premorbid state.
  - Better treatment response is usually observed in first-episode patients or early in the course of illness.
  - With subsequent relapses, recovery tends to be less complete.

**Recent studies** in patients with first-episode schizophrenia show that formulation impacts efficacy, with greater improvements observed with a long-acting injectable (LAI) antipsychotic versus an oral antipsychotic in terms of:
- Reducing time to relapse
- Improving cognition scores (as assessed by the MATRICS Consensus Cognitive Battery [MCCB]) overall composite score, \( P < 0.09 \) and in the areas of working memory (\( P = 0.08 \) and verbal learning) also clinically significant.
- Increasing intracortical myelin (ICM)

**DISEASE RECOVERY EVALUATION AND MODIFICATION (DREAM) STUDY**

**Objective**

- To examine whether an LAI with a 1-month and 3-month injection schedule can slow disease progression and possibly modify the course of schizophrenia compared to oral antipsychotics (OAs) in patients with recent-onset schizophrenia or schizophreniaiform disorder by tracking changes in cognition, functioning, and ICM volume and by tracking treatment failure.
- Disease modification is based on a totality-of-evidence approach that evaluates the course and pathophysiology of the illness with measures of symptoms, functioning, and biological changes.

**Study Design**

- **DREAM (NCT02413702)** is a prospective, matched-control, double-blind, randomized, open-label, flexible-dose study in subjects with recent-onset schizophrenia or schizophreniaiform disorder to compare disease progression and disease modification following treatment with once-monthly and once-every-3-months LAI or OA.
- **Overview of study design** (Figure 2):
  - Patients with a Diagnostic and Statistical Manual of Mental Disorders (5th ed; DSM-5) diagnosis of schizophrenia or schizophreniaiform disorder and first psychotic episode within 2 years are eligible.
- **Dynamic Disease Progression and Disease Modification**
  - Disease progression: worsening of a disease in terms of treatment's effect on symptomatic improvement and potential disease modification.
  - Disease modification: alteration of the underlying disease pathophysiology that results in a beneficial outcome.

**Assessments**

- **Primary endpoint**: time to first treatment failure in Part 2, comparing LAI and OA. Treatment failure was defined as:
  - Psychiatric hospitalization due to worsening symptoms (including emergency department visits ≥23 hours)
  - Deliberate self-injury, suicidal ideation or behavior, homicidal ideation, or violent behavior judged clinically significant
  - Increase in the level of psychiatric services in order to prevent imminent psychiatric hospitalization
  - Non-arrrest/medicantion
  - Discontinuation of antipsychotic treatment due to inadequate efficacy or a safety/tolerance issue
  - Suspension with another antipsychotic due to inadequate efficacy (including OA supplementation to LAI treatment)
  - Changes in cognition via MCCB, patient functioning (assessed with the Personal and Social Performance scale), and ICM volume (via magnetic resonance imaging) will also be assessed as measures of disease progression (in Parts 2 and 3) and modification (in Part 3).
- **A sample size of 275 subjects is planned (~50% with ICM volume follow-up).**

**Key Components of DREAM Study**

- Randomized, multicenter study comparing the impact of oral and LAI antipsychotics on:
  - Treatment failure in recent-onset schizophrenia
  - Functional outcomes in recent-onset schizophrenia
  - Cognitive performance in recent-onset schizophrenia
- **Randomized matched controls**
  - Prospective run-in with static and dynamic prognostic factors
  - 2-month run-in period will also help to identify subjects who have a propensity to discontinue treatment.
- **Randomized delayed start**
  - Verification and quantification of delayed-start effect
  - Disease modification as a clinical judgment based on the totality of evidence (ie, effect on disease progression or disease modification).

**DISCUSSION**

- **Key features of the DREAM study** include:
  - A flexible-dose run-in period in Parts 1 (collect demographic and baseline patient characteristics needed for the matched-control analysis) and 2 (identify subtypes likely to demonstrate the study, thereby reducing dropout rates during Parts 2 and 3)
  - A randomized, matched control of patients for a doubly randomized delayed start design to evaluate disease modification.
  - DREAM, to the best of our knowledge, will provide the largest dataset of ICM images acquired during treatment in a population of patients with recent-onset schizophrenia.
  - The study’s results may provide important insights into disease progression and potential disease modification in recent-onset schizophrenia and into the comparative effectiveness of LAIs and OAs used to treat this disorder.

**REFERENCES**


**Acknowledgments**

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**Disclosures**

Conflicts of interest: L. Fu, P. Alphs, D.-J. Fu are employees of Janssen Scientific Affairs, LLC, and Johnson & Johnson stockholders. I. Turkov is an employee of Janssen Research and Development, LLC, and a Johnson & Johnson stockholder.
**INTRODUCTION**

How Do Disease Progression and Disease Modification Differ?

- Disease progression: worsening of a disease in terms of symptom severity, underlying pathology, or outcome*
- Disease modification: alteration of the underlying disease pathophysiology that results in a beneficial outcome*

*The terms “disease progression” is most commonly used for chronic and incurable diseases where the stage of the disease is an important determinant of therapy and prognosis.

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- They are primarily used to evaluate treatments for slowly progressing and debilitating diseases, such as Parkinson’s disease and Alzheimer’s disease.
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  - Phase 1: patients are randomly assigned to receive active treatment or placebo. They are then followed up for an extended period of time to track disease progression and observe the effects of treatment on symptoms.
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- Better treatment response is usually observed in first-episode patients or early in the course of illness. With subsequent relapses, recovery tends to be less complete.
- Cognitive impairment and dysregulated developmental trajectory of frontal lobe myelination are enduring components of schizophrenia. However, early intervention may increase the effectiveness of treatment with antipsychotic medication, and it may mitigate biological and clinical trajectories of decline in chronic or refractory disease statuses.*

Recent studies** in patients with first-episode schizophrenia have shown that formulation impacts efficacy, with greater improvements observed with a long-acting injectable (LAI) antipsychotic versus an oral antipsychotic in terms of:

- Reducing time to relapse (Figure 1)
- Improving cognition scores (as assessed by the MATRICS Consensus Cognitive Battery (MCCB)) overall (composite score, P = 0.09) and in the areas of working memory (P = 0.08) and verbal learning (P = 0.03).
- Increasing intracortical myelin (ICM) (1)*

![Figure 1. Kaplan-Meier curve of time to relapse.](image)

**DISEASE RECOVERY EVALUATION AND MODIFICATION (DREAM) STUDY**

**Objective**

To determine whether an LAI with a 1-month and 3-month injection schedule can slow disease progression and possibly modify the course of schizophrenia compared to oral antipsychotics (OAs) in patients with recent-onset schizophrenia or schizophreniaiform disorder by tracking changes in cognition, functioning, and ICM volume and by tracking treatment failure.

**Study Design**

- **DREAM (NCT02411702)** is a prospective, matched-control, double-blind, randomized, open-label, flexible-dose study in subjects with recent-onset schizophrenia or schizophreniaiform disorder to compare disease progression and disease modification following treatment with once-monthly and once-every-3-months LAI or OA.
- **Source of study design (Figure 2):** Patients with a Diagnostic and Statistical Manual of Mental Disorders (5th ed; DSM-5) diagnosis of schizophrenia or schizophreniaiform disorder and first psychiatric episode within 2 years are eligible.

![Figure 2. Schematic of DREAM study.](image)

**Assessments**

- **Primary overall endpoint:** Time to first treatment failure in Part 2, comparing LAI and OA. Treatment failure was defined as:
  - Psychiatric hospitalization due to worsening symptoms (including emergency department visits ≥23 hours)
  - Deliberate self-injury, suicidal ideation or behavior, homicidal ideation, or violent behavior (deemed clinically relevant)
  - Increase in the level of psychiatric services in order to prevent imminent psychiatric hospitalization
  - New arrest/encarceration
  - Discontinuation of antipsychotic treatment due to inadequate efficacy or a safety/tolerability issue
  - Supplementation with another antipsychotic due to inadequate efficacy (including OA supplementation to LAI treatment)
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- In Part 3, if LAI has disease-modifying effects, the two LAI groups (immediate start and delayed start) will have similar slopes. This “failure to catch up” concept is suggested by the parallel lines and indicates disease-modifying effect (Figure 3A).
- If LAI does not have disease-modifying effects, there will be a significant decrease in the size of $\delta$, versus the start of Part 3 (B). Delayed-start treatment benefit is measured by the size of $\delta$ (Figure 3B).

**REFERENCES**


**ACKNOWLEDGMENTS**

The authors thank Matthew Graycow, PhD, and Lynn Brown, PhD, for their writing and editorial assistance.

**Disclosures**

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