

# **Model-based Approaches to Assist Clinical Development of Psychiatric Products**

**Session Chair: Hao Zhu, Ph.D.,  
Co-chair: Mitchell Mathis, M.D.,**

**ASCP Meeting  
(May, 2017)**

# Agenda

## 1. Presentation

- *Exposure-Response Analysis of Blood Pressure and Heart Rate Changes for Methylphenidate in Healthy Adults*
  - Speaker : *Yaning Wang, Ph.D.,*
- *Population Pharmacokinetic Modeling and Simulation to Determine Dosing Strategies for Long Acting Injectable Antipsychotics*
  - Speaker 2: *Hao Zhu, Ph.D.,*
- *Optimization of Short-term Schizophrenia Clinical Trials*
  - Speaker 3: *Islam Younis, Ph.D.,*

## 2. Panel Discussion

- Dr. Mitchell Mathis, M.D.,
- Dr. Yaning Wang, Ph.D.,
- Dr. Islam Younis, Ph.D.,



# Presentation

# Panel Discussion

# Multiple Choice Questions

# Question 1

*1. How can quantitative clinical pharmacology tools be used to assist clinical trial design?*

*a.) To optimize selected doses or dosing regimens.*

*b.) To design safety monitoring schedule or plan.*

*c.) To optimize trial duration.*

*d.) All of above*

Answer:

# Question 1

*1. How can quantitative clinical pharmacology tools be used to assist clinical trial design?*

*a.) To optimize selected doses or dosing regimens.*

*b.) To design safety monitoring schedule or plan.*

*c.) To optimize trial duration.*

*d.) All of above*

Answer: **d.)**

## Question 2

*2. What are the commonly used quantitative clinical pharmacology tools?*

- a.) Population pharmacokinetic modeling and simulation*
- b.) Exposure-response modeling and simulation*
- c.) Disease modeling and simulation*
- d.) All of above*

Answer:



## Question 2

*2. What are the commonly used quantitative clinical pharmacology tools?*

- a.) Population pharmacokinetic modeling and simulation*
- b.) Exposure-response modeling and simulation*
- c.) Disease modeling and simulation*
- d.) All of above*

Answer: **d.)**

# **Population Pharmacokinetic Modeling and Simulation to Determine Dosing Strategies for Long Acting Injectable Antipsychotics**

**Hao Zhu, Ph.D.**

**Clinical Pharmacology Team Leader,**

**OCP/OTS/CDER/FDA**

**ASCP Meeting**

**(May, 2017)**

# Outline

- Introduction
- Case Study
  - Invega Sustenna<sup>®</sup>
- Summary

Disclaimer:

1. I have no conflict of interest to report.
2. The views presented here are my personal views.

# Long Acting Antipsychotics

- Long acting antipsychotics (LAIs) are developed for the treatment of patients with schizophrenia and bipolar disorder for the following reasons.
  - Long term treatment is necessary for relapse prevention.
  - Less frequent dosing may improve compliance.

Brand Name	Generic Name	Indication	Maintenance Dosing intervals
Zyprexa	Onlanzapine	Schizophrenia	Once every 2 weeks or once every 4 weeks
Relprevy			
Invega Sustenna	Paliperidone	Schizophrenia	Once monthly
	Palmitate		
Invega Trinza	Paliperidone	Schizophrenia	Once every 3 months
	Palmitate		
Abilify	Aripiprazole	Schizophrenia	Once monthly
Maintena	Aripiprazole	Schizophrenia	Once monthly
Aristada	Lauroxil	Schizophrenia	Once monthly or Once every 6 weeks
Risperdal	Risperidone	Schizophrenia and	Once every 2 weeks
Consta		Bipolar I disorder	

# Challenges for Dosing a LAI



- A LAI has a long apparent half life.
  - Apparent half life may affect the following factors.
    - Time to reach steady state.
    - Time for disappearance of a drug.
  - How to rely on previous clin pharm findings of a different formulation (IR or ER).
- As a result, to define appropriate dosing strategies for a LAI is challenging.
  - Loading dose.
  - Dosing window.
  - Reinitiation dosing for patients discontinued at different intervals
  - Dosing in patients with compromised organ dysfunction or receiving concomitant medications.

# Benefits for Modeling and Simulation

- Clinical trials
  - Costly and time-consuming
  - Sometimes, unethical or impractical
    - E.g., Re-initiation dosing regimens for patients discontinuing the treatment with different intervals.
- Modeling and simulation.
  - Pools the pharmacokinetic information together and provides a reasonable tool to assess the exposure and PK profile changes under different scenarios.

# Case Study: Invega Sustenna

NDC 50458-563-01  
For Single Use Only - Use Entire Content of Syringe


**INVEGA® SUSTENNA®**  
paliperidone palmitate **156 mg**  
extended-release  
injectable suspension

**156 mg**  
Each 1 mL prefilled syringe contains  
156 mg paliperidone palmitate

FOR INTRAMUSCULAR INJECTION ONLY  
Shake before using Rx Only

CONTENTS: 1 prefilled syringe and 2 needles  
(a 22G, 1½-inch safety needle and a 23G, 1-inch safety needle)

For initiation and monthly maintenance dosing  
instructions, please see accompanying full  
Package Insert.

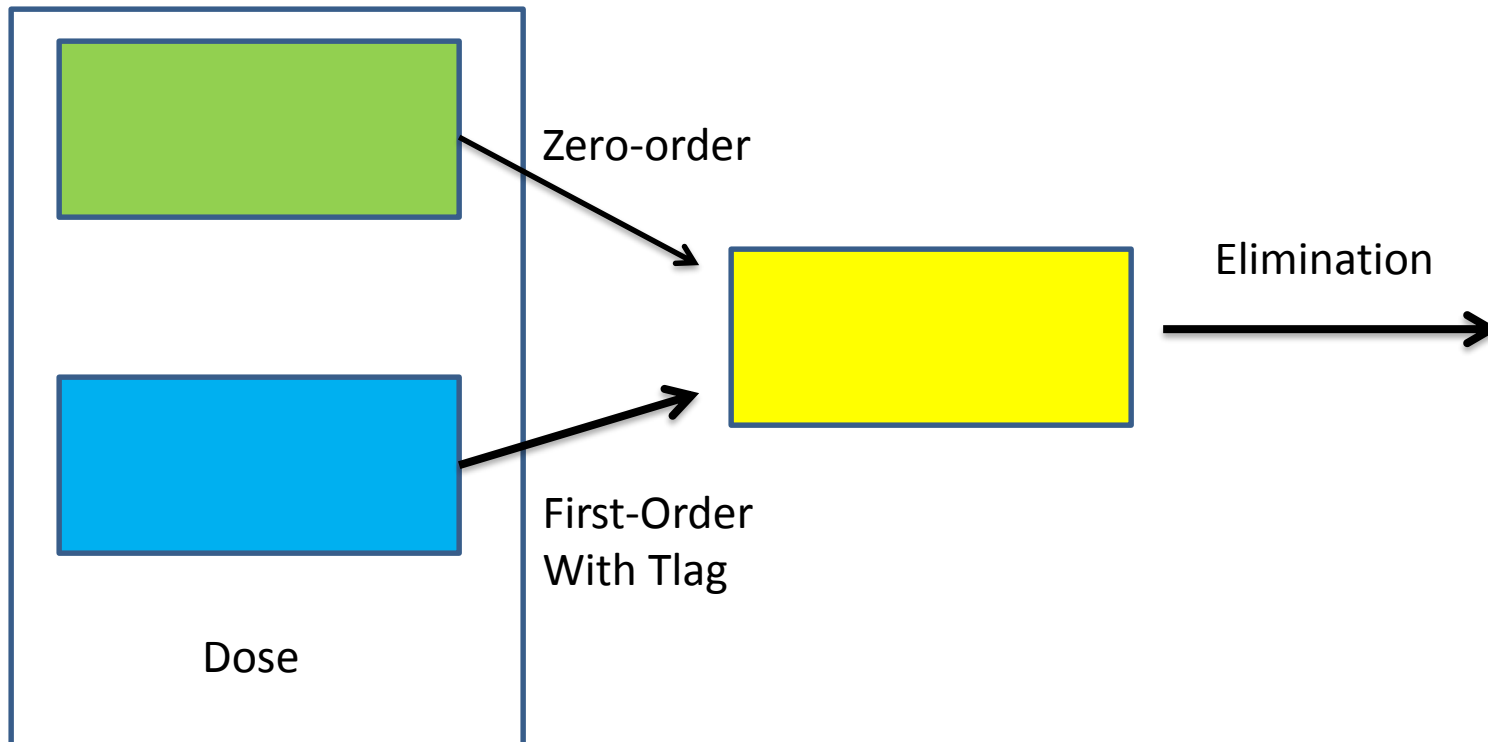
janssen 



- Invega Sustenna [\*Ref 1]: (Approved in 2006)
  - The brand name for paliperidone palmitate indicated for the treatment of schizophrenia and schizoaffective disorder.
- Dosing regimens (All supported by Modeling and simulations):
  - Loading dose: 234 mg on Day 1 and 156 mg on Day 8.
  - Recommended maintenance dose: 117 mg Q 4 weeks.
  - Maintenance dose range: 39-234 mg (for schizophrenia)
  - Switching from oral paliperidone formulation: The same loading dose regimen is recommended for patients switching from oral formulation of paliperidone.
  - Switching from risperidone LAI: Continue with the Invega Sustenna injection without a loading dose.
  - Dosing window:
    - 2<sup>nd</sup> Dose:  $\pm$  4 days.
    - Maintenance Dose:  $\pm$  7 days.
  - Missing doses (Different strategies applied for different missing intervals):
    - Loading dose: < 4 weeks, 4-7 weeks, > 7 weeks.
    - Maintenance dose: 4-6 weeks, 6 weeks – 6 months, > 6 months
  - Dosage adjustment:
    - Mild renal impairment: 156 mg on Day 1 with 117 mg on Day 8, followed by a maintenance dose of 78 mg Q 4 weeks



# Pop-PK Model

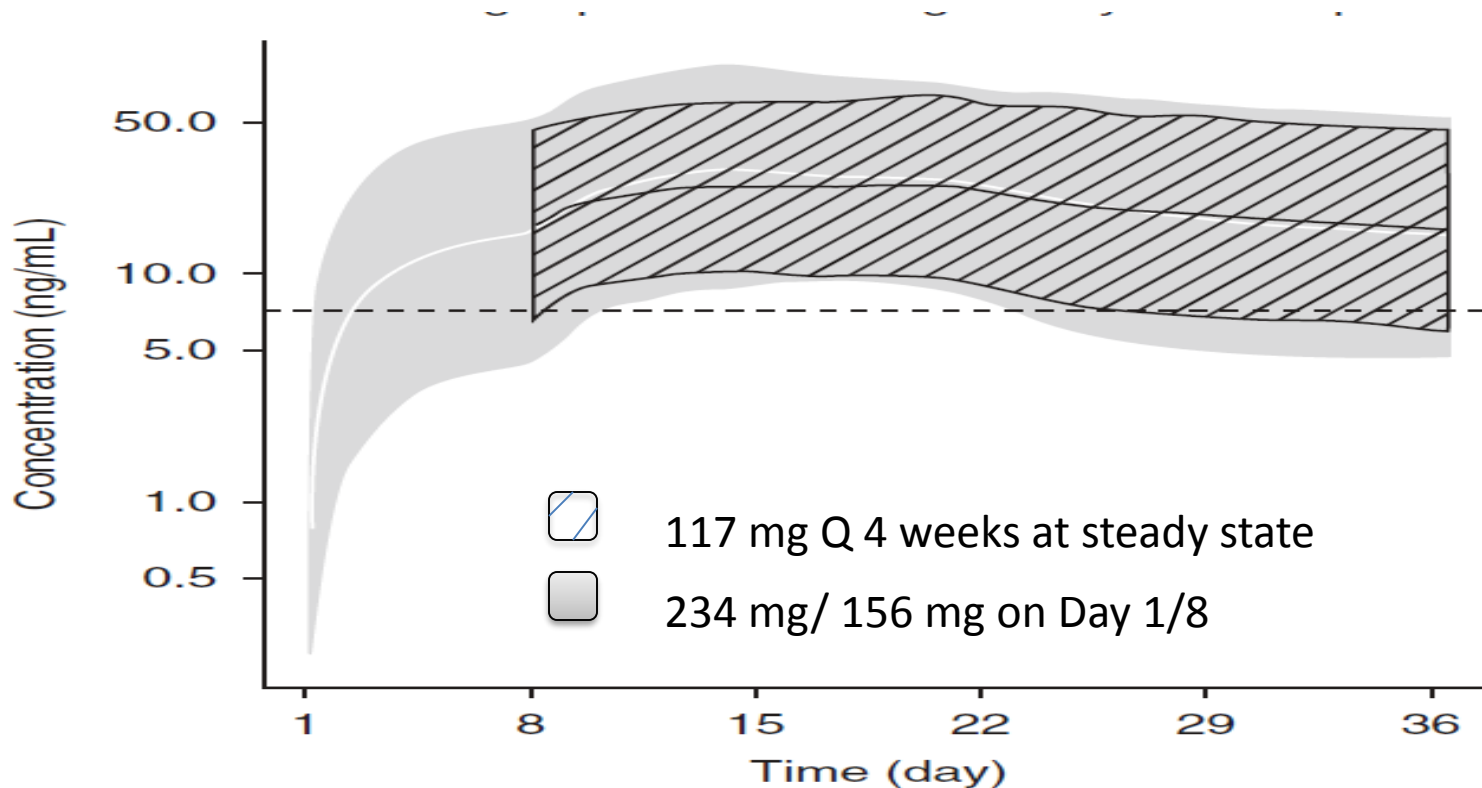


## Pop-PK Model:

- A fraction of the drug is absorbed at a constant rate.
- The rest of the drug is absorbed following a first-order process with a delayed time.
- The drug is eliminated following a first-order process.

# Loading Dose Determination

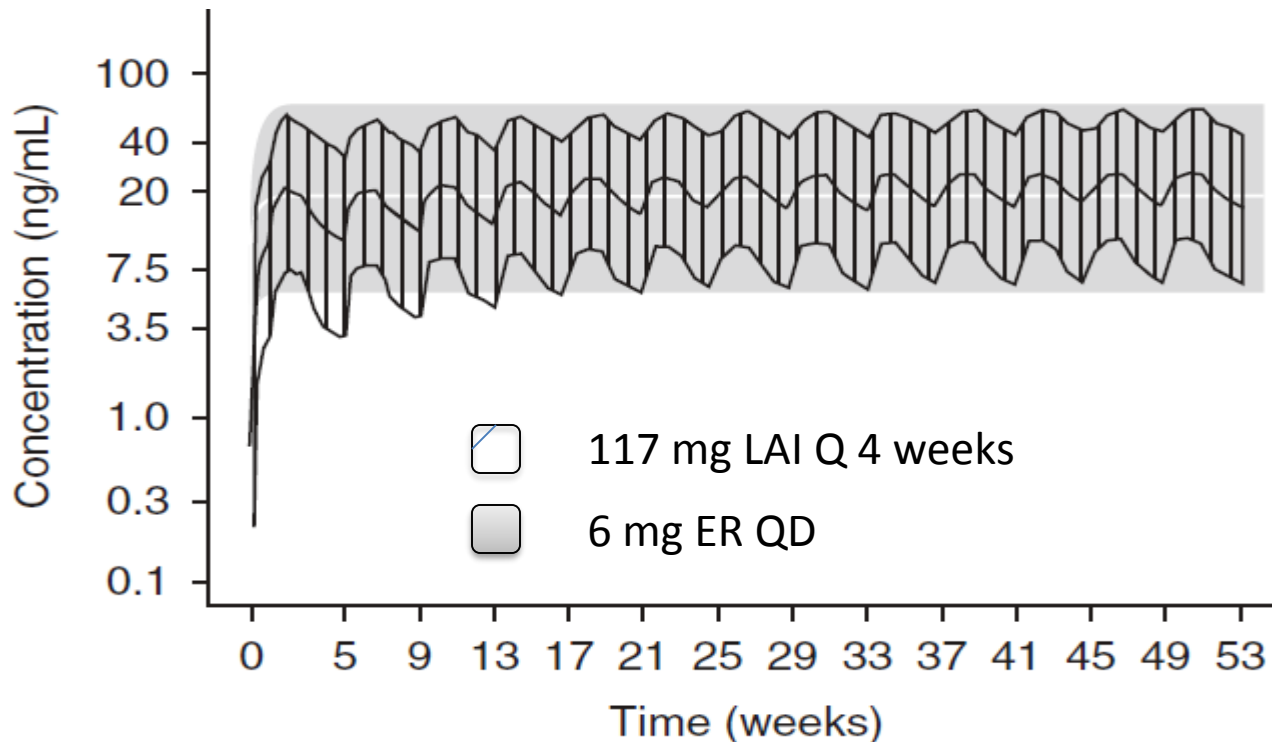
Within a week, the loading dose of 234 mg on Day 1 and 156 mg on Day 8 brings the exposure similar to the steady state exposure for 117 mg Q 4 weeks.



Simulated PK Profile with Median and 90% Prediction Intervals \*[Ref 2]

# Maintenance Dosing Regimen

Following the maintenance dose of 39-234 mg Q 4 weeks, the exposure ranges are similar to the steady state exposure range following a ER formulation with 2-12 mg QD.

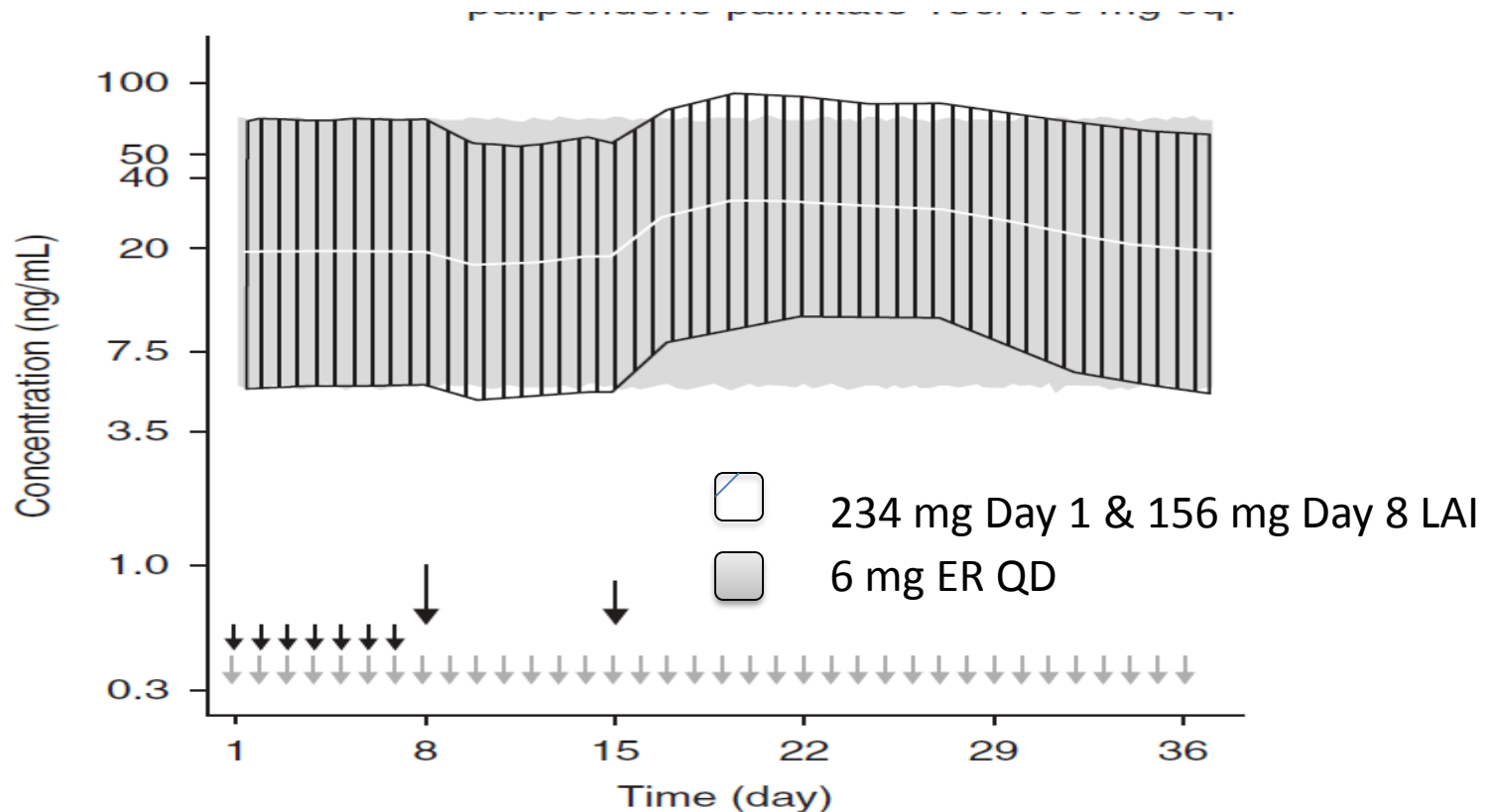


Simulated PK Profile with Median and 90% Prediction Intervals \*[Ref 2]

# Switching from Oral Paliperidone



Loading dose with 234 mg on Day 1 and 156 mg on Day 8 is necessary to ensure the exposure can be maintained for patients stabilized with 6 mg oral dose.

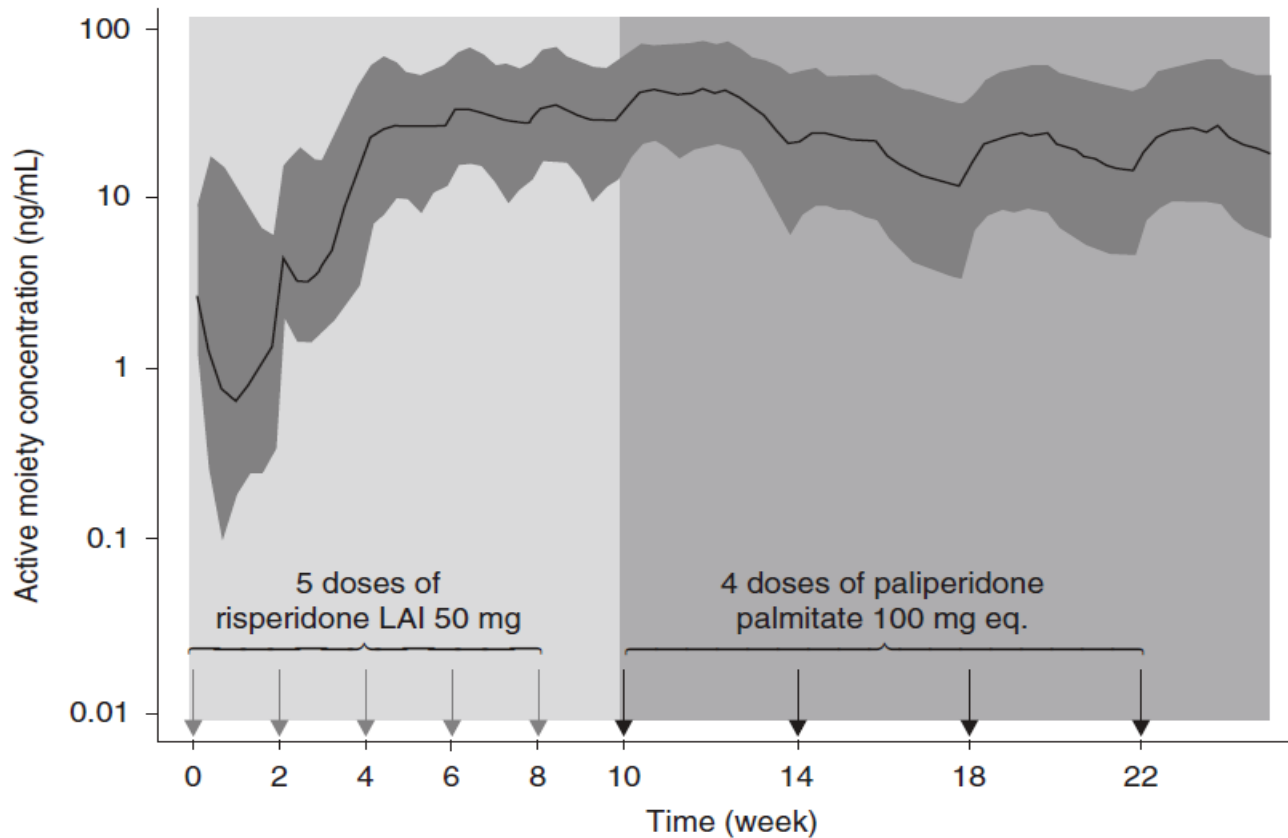


Simulated PK Profile with Median and 90% Prediction Intervals \*[Ref 2]

# Switching from Risperidone LAI



No loading dose is necessary for switching from risperidone LAI to Paliperidone LAI

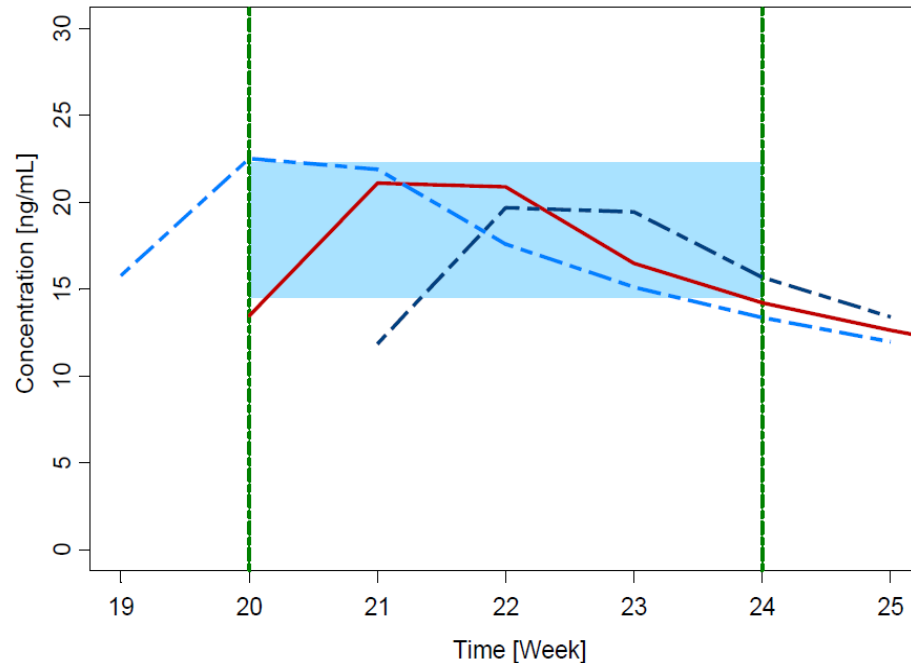


Note:  
Paliperidone  
Palmitate 100 mg  
eq. = Paliperidone  
Palmitate 117 mg

Simulated PK Profile with Median and 90% Prediction Intervals \*[Ref 2]

# Dosing Windows on Maintenance Dose

## ( $\pm 7$ days)

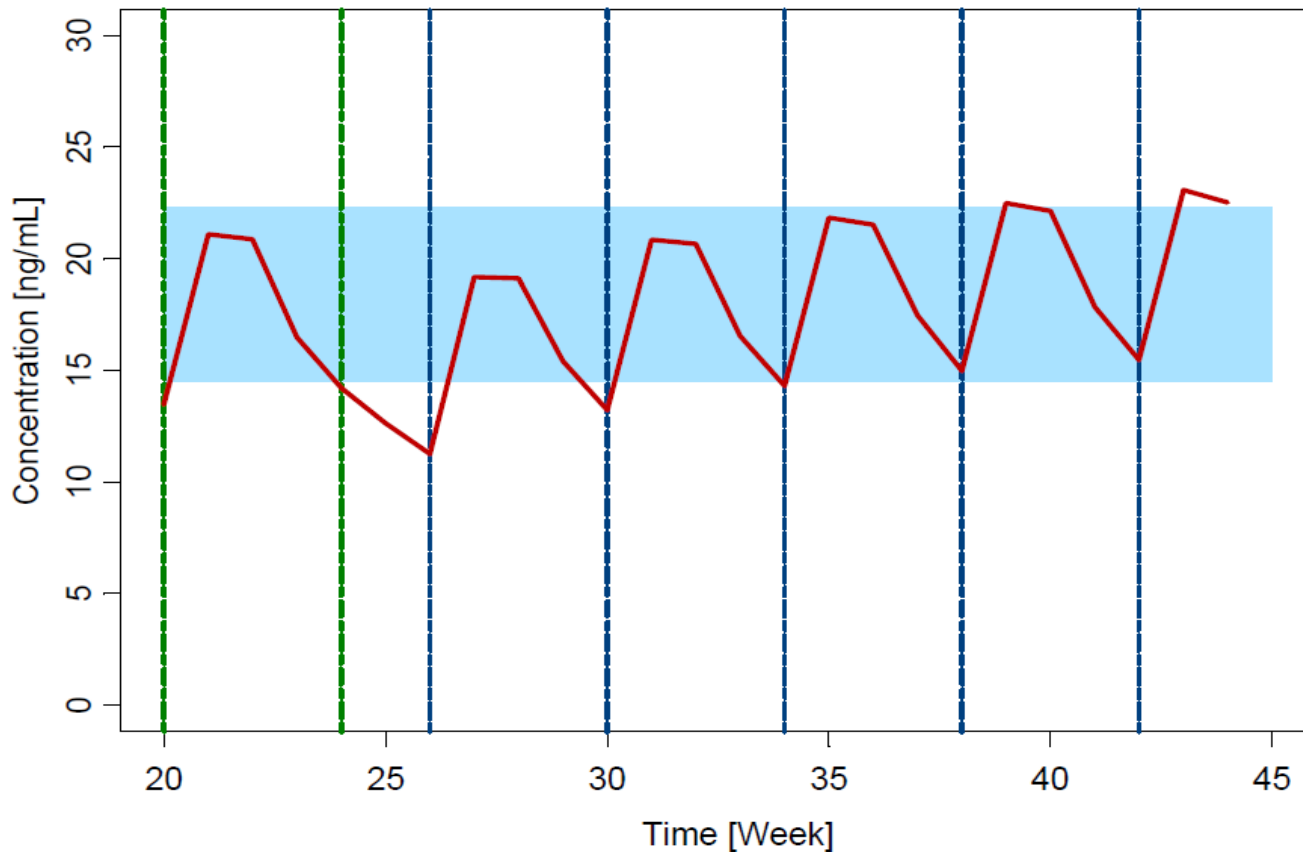


Note:

1. Dashed light blue line = Maintenance dose given 1 week prior to the scheduled visit
2. Red line = Maintenance dose given on time.
3. Dashed dark blue line = Maintenance dose given 1 week after the scheduled visit

Mean concentration-time profiles (lines) as compared to the expected exposure levels (blue box) [Ref 3].

# Missing doses – 4-6 weeks



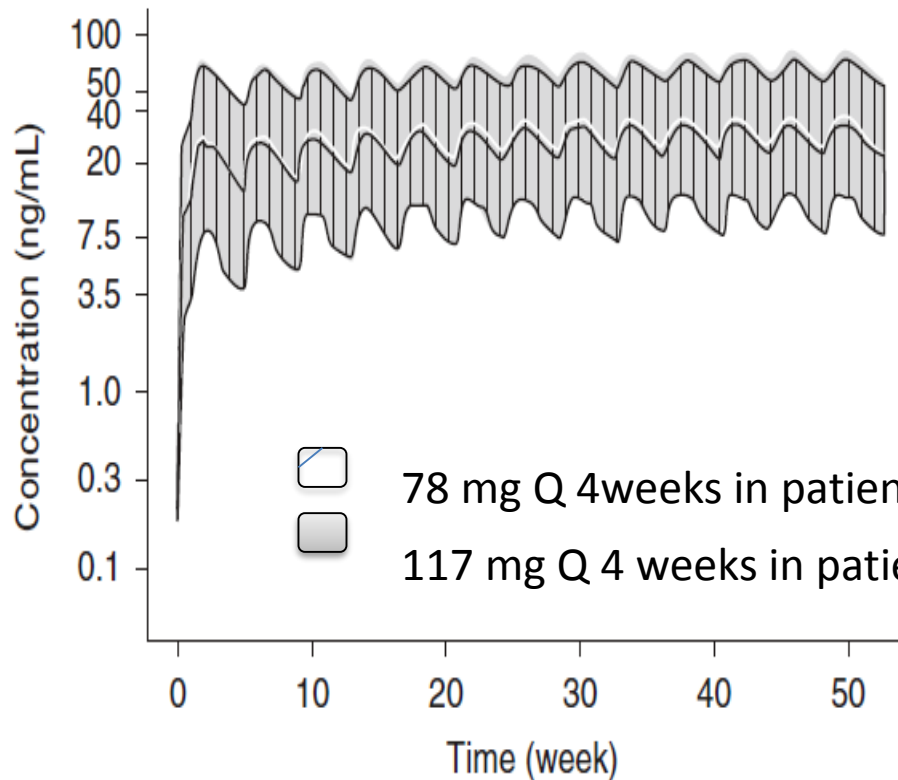
Note:

1. Green lines = regular dosing interval
2. Blue lines = adjusted dosing intervals.

Regimen: resume the with previously stabilized dose, followed by injections at monthly interval.

Mean PK profile (Red line) for patients missing 4-6 weeks receiving the recommended reinitiation dosing as compared to the expected exposure levels (blue box) . [Ref 3]

# Dosage adjustment in Mild Renal Impairment Patients



## Note:

- ~ 60% of paliperidone is excreted by kidney.
- A maintenance dose of 78 mg in mild renal impairment patients yields exposure similar to that under 117 mg in patients with normal renal function



Brand Name	Generic Name	Dosing Window	Missed Dose	Reinitiation Regimen	Organ Dysfunction/ DDI	Switching from Oral formulation
Invega Sustenna	Paliperidone	✓	✓	✓	✓	✓
Invega Trinza	Paliperidone	✓	✓	✓	✓	✓
Abilify Maitenna	Aripiprazole	✓	✓	✓	✓	✓
Aristada	Aripiprazole	✓	✓	✓	✓	✓

# Summary

- Modeling and simulation is a useful tool to support/derive dosing for patients under various scenarios.
  - Loading dosing regimens
  - Flexible dosing window
  - Dosing with DDIs
  - Dosing in patients with compromised organ function.
  - Re-initiation dosing.
  - Dosing for switching products
- This tool has been applied to support dosing regimens for multiple long acting injections, such as Invega Sustenna<sup>®</sup>, Invega Trinza<sup>®</sup>, Abilify Maintenna<sup>®</sup>, and Aristada<sup>®</sup>.



# Acknowledgement

- DCP1: Dr. Mehul Mehta, Dr. Ramana Uppoor, Dr. Praveen Balimane, Dr. Kofi Kumi, and Dr. Huixia Zhang
- DPM: Dr. Yaning Wang, Dr. Kevin Krudys, Dr. Xiaofeng Wang,
- DPP: Dr. Mitchell Mathis, Dr. Tiffany Farchione
- Previous FDA colleagues: Dr. Thomas Laughren , Dr. Satjit Brar



# Reference

1. U.S. Package insert of Invega Sustenna<sup>®</sup>.

[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/022264s019lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022264s019lbl.pdf).

2. [Samtani MN](#), [Gopal S](#), [Gassmann-Mayer C](#), [Alphs L](#), [Palumbo JM](#). Dosing and switching strategies for paliperidone palmitate: based on population pharmacokinetic modelling and clinical trial data. [CNS Drugs](#). 2011 Oct 1;25(10):829-45

3. Clinical Pharmacology review of Invega Sustenna<sup>®</sup>.

[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2009/022264s000clinpharmr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf).