U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Modeling and Simulation for Long-Acting Psychotic Products

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Disclaimer:
1. I have no conflict of interest to report.
2. The views expressed are my personal views and may not represent the position of the US FDA.

Outline

- **Background & Introduction**
  - Long acting injectables (LAIs) for patients with psychiatric diseases
  - Available LAIs
- **Modeling and Simulation for LAIs**
  - Role of M&S for LAIs
    - To support approval of new strengths (or new dosing regimens)
    - To support new dosing regimens
    - To optimize dosing regimes in subgroups
  - Case Study 1: New Strengths - Aristada ®
  - Case Study 2: New Dosing Regimens - Invega Sustenna ®
  - Case Study 3: Optimize Dosing Regimens in Subgroups – Invega Sustenna ® and other LAIs
- **Take Home Messages**

Background

- Psychiatric diseases, such as schizophrenia and bipolar disorder, are severe debilitating mental disorders affecting patients' daily function and social interaction.
- Long-acting injectable (LAI) anti-psychiatric products have been developed & marketed in recent years.
  - Chronic treatment is essential to prevent relapse and to control symptoms.
  - Compliance is a common problem in patients with schizophrenia or bipolar disorder.

Introduction

Examples of Marketed Long-Acting Injectable Anti-psychotics

Compound	Product	Dosing Regimen
Aripiprazole	Abilify Maintena ®	400 mg + 10/20 mg oral daily × 14 days & 400 /300 mg Q monthly
Aripiprazole Lauroxil	Aristada ® Aristada Initio ®	(1) Aristada Initio® 675 mg + 30 mg oral + Aristada® × 1 (2) Aristada ® + oral × 21 days & 441, 662, 882 mg Q monthly, or 882 mg Q 6 Wk, or 1064 mg Q 2 months.
Olanzapine	Zyprexa Relprevv ®	150, 210, 300 mg Q 2Wk, or 300, 405 mg Q 4Wk
Paliperidone	Invega Sustenna ®	234 mg day 1 + 156 mg day 8 & 39 – 234 mg Q monthly
Paliperidone	Invega Trinza ®	273 – 819 mg Q 3 months (Following Invega Sustenna ® for at least
Risperidone	Risperdal Consta ®	25 mg Q 2 Wk

Modeling and Simulation for LAIs

- To support approval of new strengths (& new dosing regimens).
- To optimize dosing regimens.
- To adjust dosing regimens in patient subgroups.

Case Study 1: New Strength (1)

Slow dissolution consistent with the ***particle size*** and ***low solubility***.

- Aripiprazole lauroxil is a prodrug that forms the active metabolite, aripiprazole.
- It is a pre-filled syringe.
- Indicated for the treatment of schizophrenia in adults

*: Aristada ® U.S. Package Insert

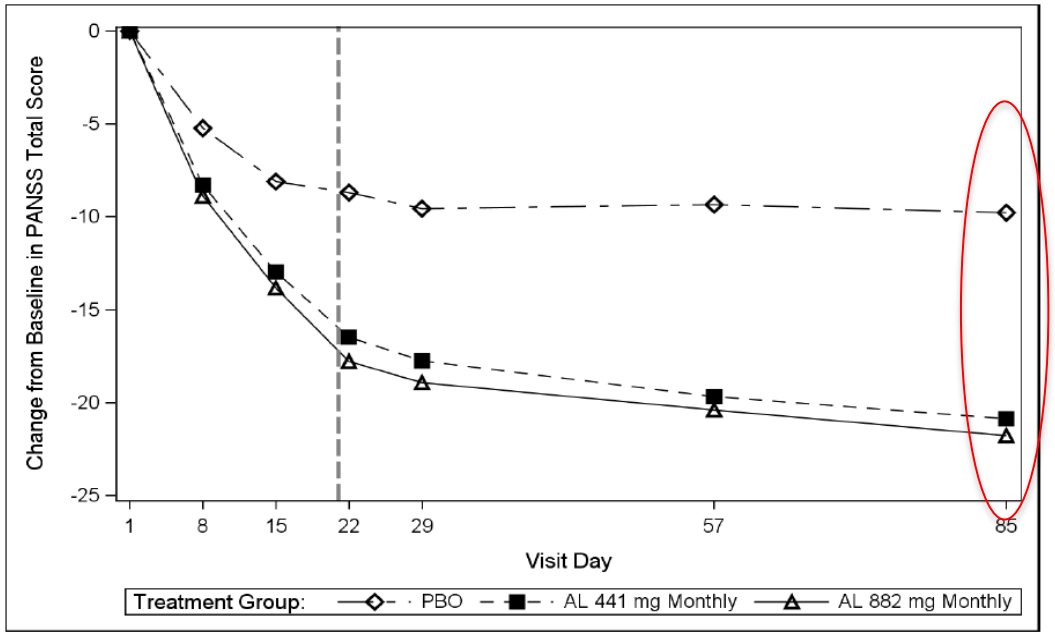
ADME Features

Process	Key Features
Absorption	T_{lag} = 5-6 days, T to SS = 4 months Or supplement with oral dose × 21 days
Distribution	Vd= 268 L, 99% binds to serum proteins,
Metabolism	Enzyme-mediated hydrolysis
Excretion	T ½ = 54 – 57 days

Case Study 1: New Strength (2)

Efficacy of Aristada ®: ***Flat Dose/Exposure-Response Relationship***

- **Efficacy data from oral aripiprazole**
- **Clinical Trial: A 12-week, randomized, double-blinded, placebo-controlled, fixed-dose study in schizophrenia patients [Aristada 441 mg, 207; Aristada 882 mg 208; Placebo 207]**



Study Number	Treatment Group	Primary Efficacy Measure: PANSS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ARISTADA 441 mg monthly[b]	92.6 (10.2)	-20.9 (1.4)	-10.9 (-14.5, -7.3)
	ARISTADA 882 mg monthly[b]	92.0 (10.8)	-21.8 (1.4)	-11.9 (-15.4, -8.3)
	Placebo	93.9 (11.3)	-9.8 (1.4)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiple comparisons.

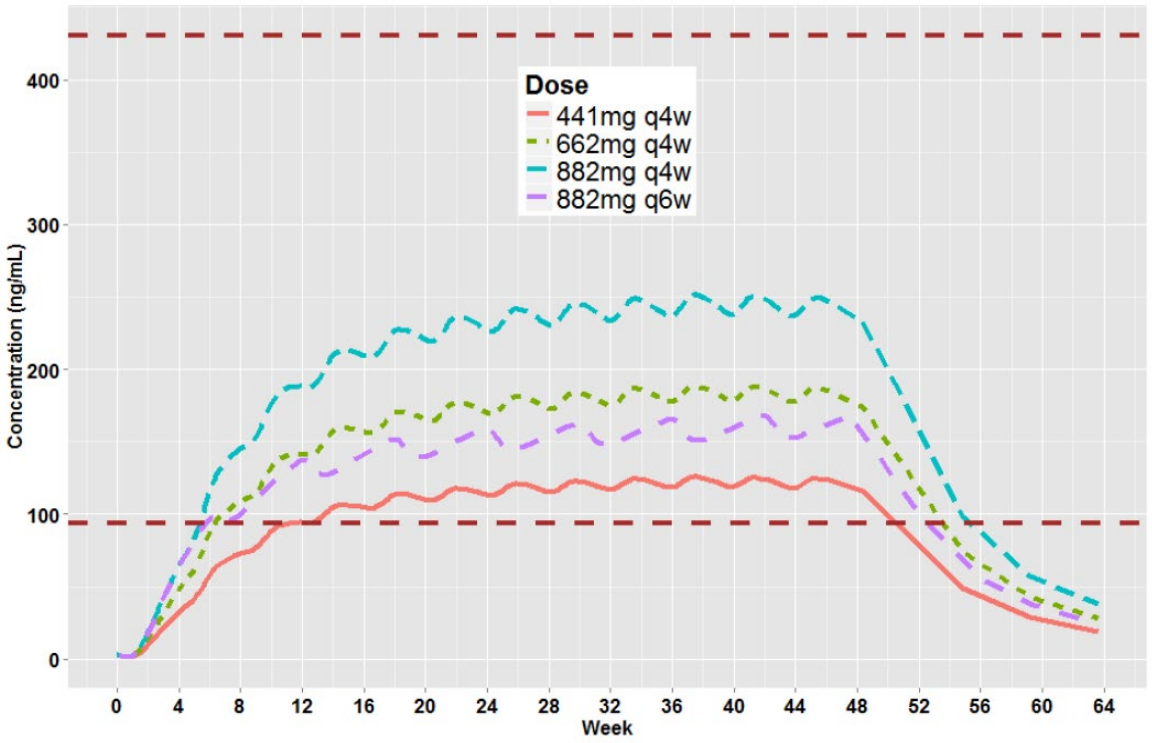
[a] Difference (drug minus placebo) in least-squares mean change from baseline.

[b] Doses that are demonstrated to be effective.

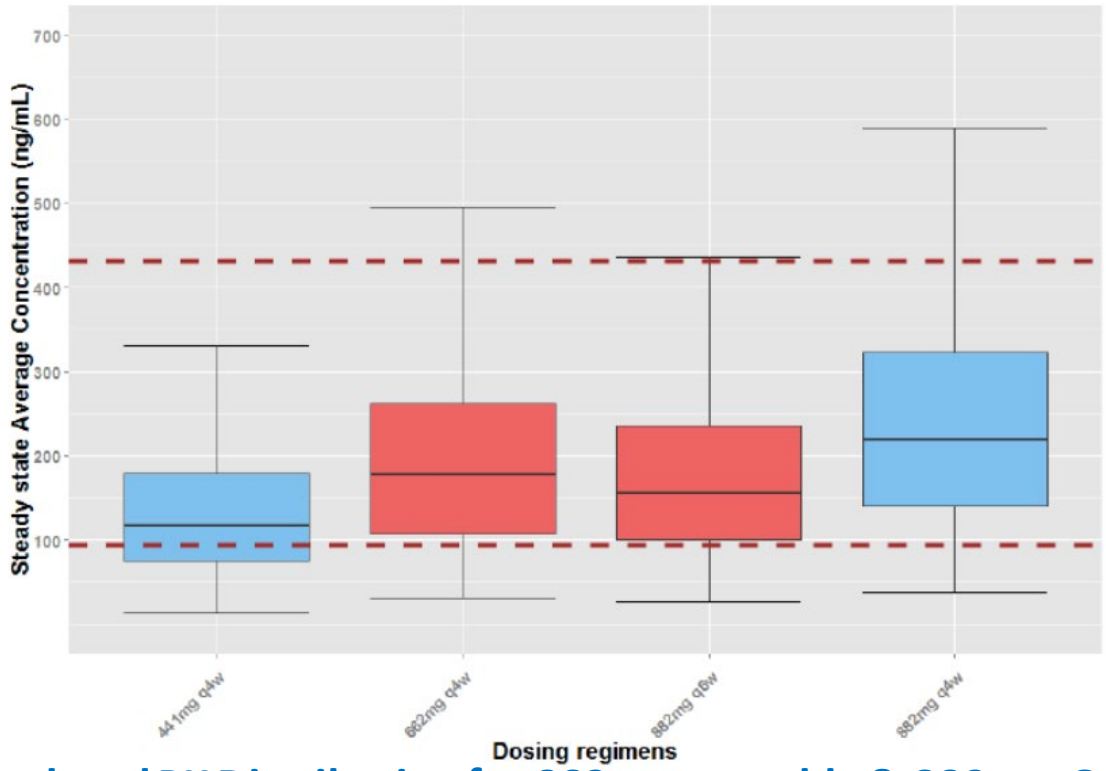
Abbreviations: AL= ARISTADA; PBO=placebo; PANSS=Positive and Negative Syndrome Scale.
Vertical dotted line indicates end of oral supplementation.

Case Study 1: New Strength (3)

- Initially approved doses include: **441 mg monthly, 882 mg monthly. + 662 mg monthly + 882 mg Q 6 Wks [662 mg is an untested strength]**



Simulated PK for 662 mg monthly & 882 mg Q 6 Wks



Simulated PK Distribution for 662 mg monthly & 882 mg Q 6 Wks

Aristada ® OCP review: <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207533Orig1s000ClinPharmR.pdf>

Case Study 1: New Strength (4)

- Similar strategy has been applied to justify one additional strength (one additional dose)

  1064 mg Q 2 months

- Final approvals:
  - Strength: 441, 662, 882 or 1064 mg single-dose pre-filled syringe.
  - Dose: 441, 662, 882 monthly, 882 mg Q 6 Wks, or 1064 mg Q 2 months.
- Labeling: (Section 14)

Efficacy of ARISTADA 662 mg Monthly, 882 mg Every 6 Weeks and 1064 mg Every 2 Months

The efficacy of ARISTADA 662 mg monthly, 882 mg every 6 weeks, and 1064 mg every 2 months in the treatment of adults with schizophrenia was established by pharmacokinetic bridging which demonstrated that these dosing regimens resulted in plasma aripiprazole concentrations that are within the range provided by doses of 441 mg monthly and 882 mg monthly. As depicted in Figure 6, the doses of 441 mg monthly and 882 mg monthly showed clinical responses similar to each other in the ARISTADA placebo-controlled trial.

Case Study 2: Dosing Regimen (1)

Slow dissolution consistent with the ***particle size*** and ***low solubility***.

Paliperidone palmitate is an LAI:

- Indicated for the treatment of schizophrenia and schizoaffective disorder in adults

*: Invega Sustenne® U.S. Package Insert

ADME Features

Process	Key Features
Absorption	T max = 13 days, A single dose releases the drug from Day 1 to Day 126.
Distribution	Vd= 391 L, protein binding = 74%
Metabolism	Paliperidone palmitate hydrolyzed into paliperidone.
Excretion	59% of the dose excreted into urine as unchanged drug. T ½ = 25-49 days

Case Study 2: Dosing Regimen (2)

- Short-term schizophrenia trials (Section 14 of the U.S. package insert)

Clinical Trial	Dosing
Study 1	3 dose groups: (234 mg + 39 mg Q 4 Wk, 156 mg Q 4 Wk, or 234 mg Q 4 Wk) vs. Placebo
Study 2	3 dose groups: (78 mg Q 4 Wk, 156 mg Q 4 Wk, 234 mg Q 4Wk) vs. Placebo
Study 3	3 dose groups: (39 mg Q 4 Wk, 78 mg Q 4 Wk, 156 mg Q 4 Wk) vs. Placebo
Study 4	2 dose groups: (78 mg Q 4 Wk, 156 mg Q 4 Wk) vs. Placebo

Note: Study 2-3 included only **maintenance doses**. Study 1 included ***1*** loading dose + **maintenance doses**.

Case Study 2: Dosing Regimen (3)

Study Number	Treatment Group	Primary Efficacy Measure: PANSS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	INVEGA SUSTENNA® (39 mg/4 weeks)*	86.9 (11.99)	-11.2 (1.69)	-5.1 (-9.01, -1.10)
	INVEGA SUSTENNA® (156 mg/4 weeks)*	86.2 (10.77)	-14.8 (1.68)	-8.7 (-12.62, -4.78)
	INVEGA SUSTENNA® (234 mg/4 weeks)*	88.4 (11.70)	-15.9 (1.70)	-9.8 (-13.71, -5.85)
	Placebo	86.8 (10.31)	-6.1 (1.69)	--
Study 2[b]	INVEGA SUSTENNA® (78 mg/4 weeks)	89.9 (10.78)	-6.9 (2.50)	-3.5 (-8.73, 1.77)
	INVEGA SUSTENNA® (156 mg/4 weeks)*	90.1 (11.66)	-10.4 (2.47)	-6.9 (-12.12, -1.68)
	Placebo	92.4 (12.55)	-3.5 (2.15)	--
Study 3	INVEGA SUSTENNA® (39 mg/4 weeks)*	90.7 (12.25)	-19.8 (2.19)	-6.6 (-11.40, -1.73)
	INVEGA SUSTENNA® (78 mg/4 weeks)*	91.2 (12.02)	-19.2 (2.19)	-5.9 (-10.76, -1.07)
	INVEGA SUSTENNA® (156 mg/4 weeks)*	90.8 (11.70)	-22.5 (2.18)	-9.2 (-14.07, -4.43)
	Placebo	90.7 (12.22)	-13.3 (2.21)	--
Study 4	INVEGA SUSTENNA® (78 mg/4 weeks)*	88.0 (12.39)	-4.6 (2.43)	-11.2 (-16.85, -5.57)
	INVEGA SUSTENNA® (156 mg/4 weeks)*	85.2 (11.09)	-7.4 (2.45)	-14.0 (-19.51, -8.58)
	Placebo	87.8 (13.90)	6.6 (2.45)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

[b] Because an insufficient number of subjects received the 234 mg/4 weeks dose, results from this group are not included.

* $p<0.05$ (Doses statistically significantly superior to placebo).

3 doses were superior to placebo

156 mg Q 4 Wk was superior to placebo

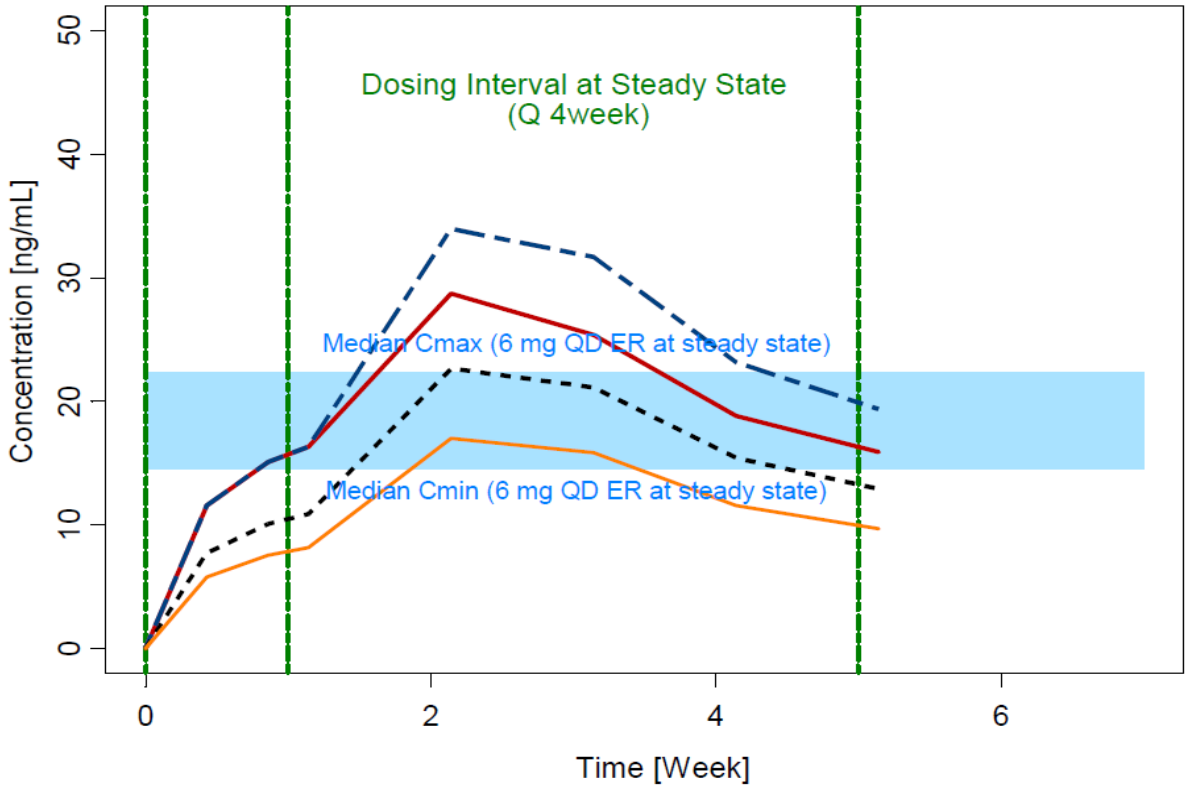
3 doses were superior to placebo

2 doses were superior to placebo

Case Study 2: Dosing Regimen (4)

- Approved Dosing Regimen: **234 mg Day 1 + 156 mg Day 8 + 39 – 234 mg Monthly**

PK Simulation to assess the initial dosing regimens



Approved Dosing Regimen

Target Exposure Range

Safety margin (Study 3007):
150 mg (Day 1) + 150 mg (Day 8)

Alternative initial dosing regimens

75 mg (Day1) + 75 mg (Day8)

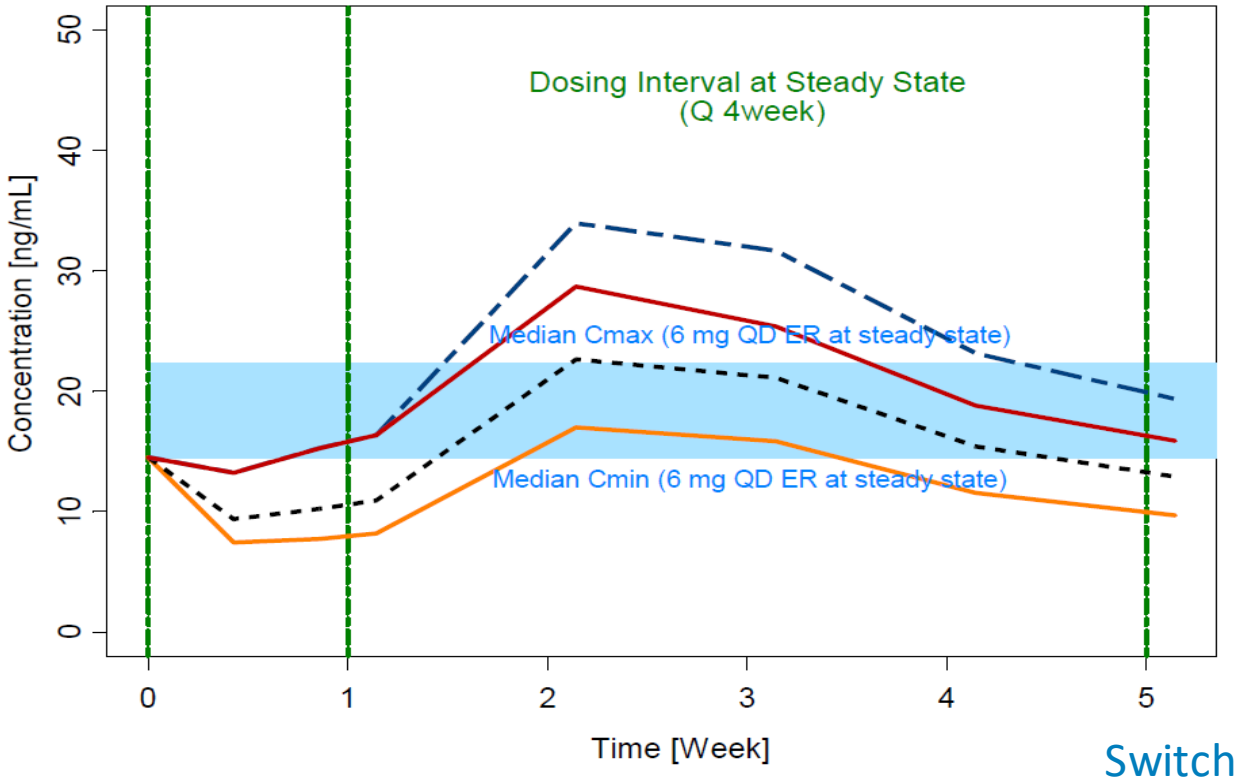
100 mg (Day 1) + 100 mg (Day 8)

No initial treatment (i.e., $C_0 = 0$), desirable exposure can be achieved by the end of the first week.

Invega Sustenna OCP review <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf>

Case Study 2: Dosing Regimen (5)

PK Simulation to assess the initial dosing regimens



Approved Dosing Regimen

Target Exposure Range

Safety margin (Study 3007):
150 mg (Day 1) + 150 mg (Day 8)

Alternative initial dosing regimens

75 mg (Day1) + 75 mg (Day8)

100 mg (Day 1) + 100 mg (Day 8)

Switching from a stable treatment (i.e., C_0 = C trough), desirable exposure can be achieved within the first week.

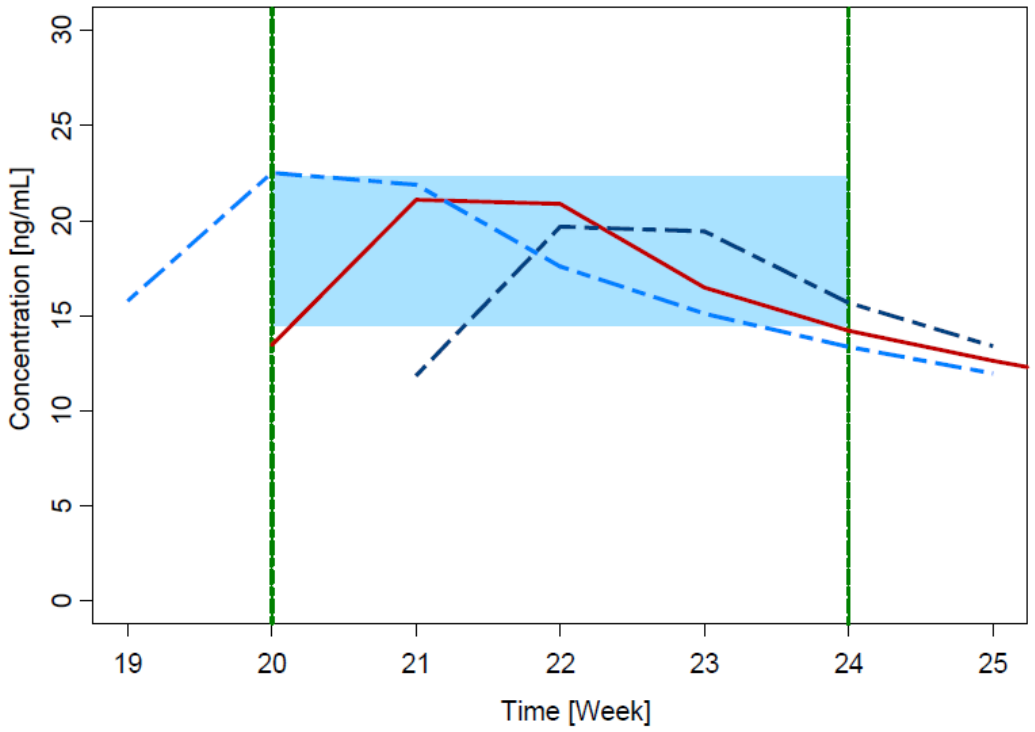
Invega Sustenna OCP review <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf>

Case Study 3: Optimize Dosing in Subgroups

- M&S may be applied to optimize dosing in patient subgroups.
  - Evaluation dosing window.
  - Dosing for patients with missing doses.

- To test these scenarios through clinical trials or even PK studies may be challenging or unethical.

Alternative Window for Maintenance Dosing



Scheduled dosing

Dosing 1 week earlier

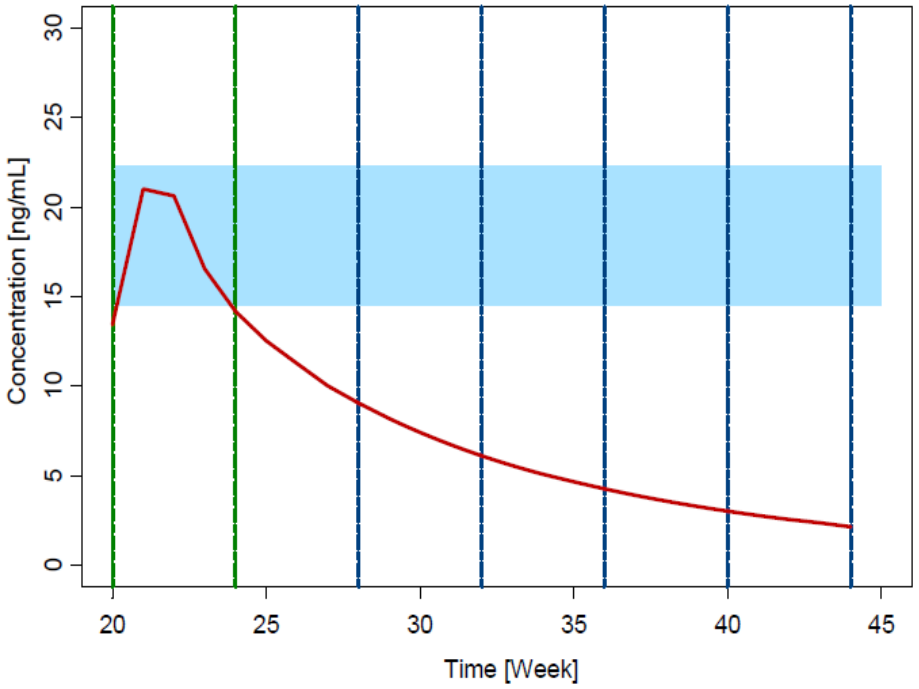
Dosing 1 week later

Acceptance range

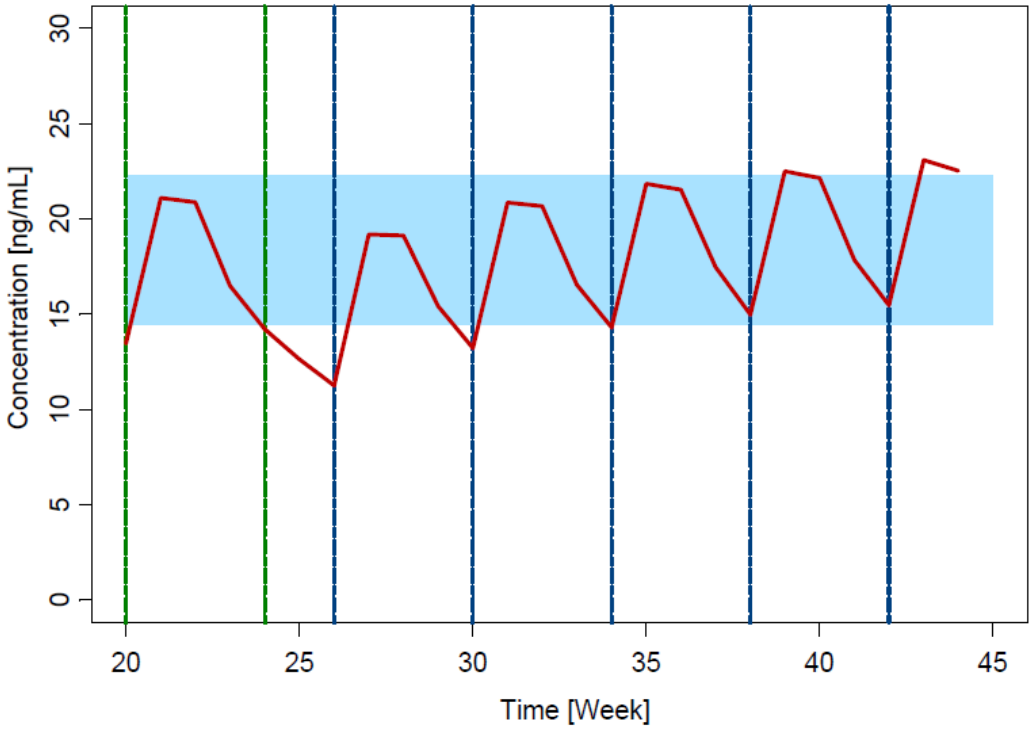
PK Simulation for assessing alternative dosing window for maintenance dosing

Invega Sustenna OCP review <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf>

Reinitiation of Treatment for Patients with Missing Doses



With no reinitation



With proposed reinitiation

To assess reinitation of treatment for patients with missing dose between 6 weeks to 6 months

Take Home Message

- Modeling and simulation are essential tools to facilitate the development of long-acting injectable products.
  - support approval of new strengths (& new dosing regimens).
  - To optimize dosing regimens.
  - To adjust dosing regimens in patient subgroups.

Acknowledgement

- Dr. Yaning Wang
- DPM Colleagues
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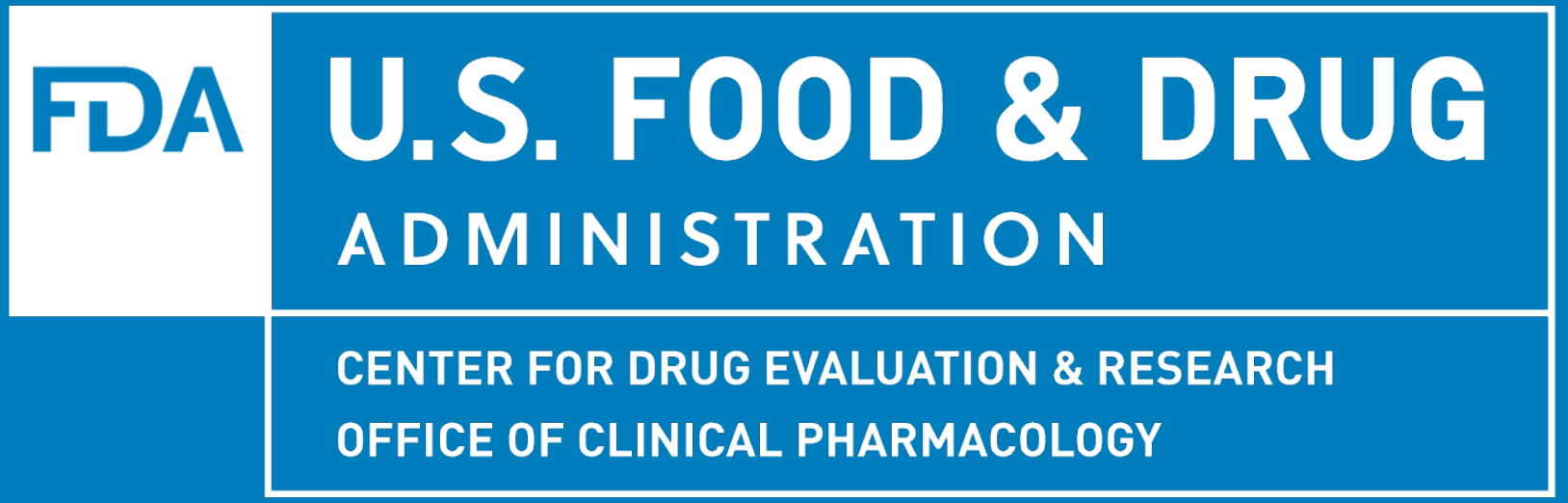
- OCP Colleagues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