The Role of Modeling and Simulation in Obesity – Evaluating the Effects on Drug Disposition and Efficacy in Adult Patients

FDA/M-CERSI Public Workshop

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Disclaimer: This presentation reflects the views of the author and should not be construed to represent official FDA policy
Outline

• Background Information
  – Precision Medicine, Intrinsic Factors, and Body Weight
• MIDD and Regulatory Avenues
• Case Examples
  – Semaglutide
• Take Home messages
Precision Medicine

Appropriate Treatment (Therapy, Combination Therapy, etc)

Appropriate Dosing: (Dose, Frequency, Duration, etc)
Heterogenous Populations

Intrinsic Factors:
(Permanent Difference)
- Age (pediatrics & geriatrics)
- Renal function
- Hepatic function
- Race/gender
- Disease severity
- Genomics
- Biomarker
- Body weight

Extrinsic Factors:
(Temporary Difference)
- DDI:
  - PK related changes
  - PD related changes
- Food / Alcohol
  - PK related changes
  - PD related changes
Body Weight Shifting

The average body weight for U.S. male and female population is higher than that 20 years ago.

Courtesy by: Dr. Ye Xiong
Diseases

Type 2 Diabetes
- Impairment in the way the body regulates and uses sugar.
- A close association between obesity and Type 2 diabetes.
  - The likelihood and severity of Type 2 diabetes are closely linked with body weight index (BMI).
  - There is a seven times greater risk of diabetes in obese people compared to those with normal weight.

Binge Eating Disorder
- It is a mental health problem. Patients feel out of control and eat a large amount of food at one time (called a binge).
- Most Binge eating patients are overweighted or obese.
High body weight (i.e., Obesity) may:
• change drug exposure
• suggest different disease severity
• be associated with changes in drug response (e.g., reduced sensitivity)
MIDD – Model Informed Drug Development

**Technical Concept:**
Application of a broad range of quantitative models to facilitate drug development and decision making.

**Regulatory Tool:**
To promote early interaction between the drug developers and FDA on key issues. (MIDD Paired Meeting Program)
Model-Informed Drug Development

Development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to address drug development or regulatory issues*

* From PDUFA 6; Excludes statistical designs involving complex adaptations, Bayesian methods, or other features requiring computer simulations to determine the operating characteristics of a confirmatory clinical trial.

To Support appropriate usage of a drug in a specific population

Huang SM 2019 AAPS
INPUT
(e.g., PK, PD, ADME, other data sources)

MIDD

OUTPUT
e.g., in silico trials, clinical & disease models)
can be used as supportive evidence for efficacy,
dose optimization, clinical trial design

Disease Model
E/R
PBPK
PK/PD
PopPK
QSP
MBMA
AI/ML

ADME, Absorption, Distribution, Metabolism, Excretion
E/R, Exposure/Response
MIDD, Model-Informed Drug Development
PBPK, Physiologically Based Pharmacokinetic Modeling
PK/PD, Pharmacokinetic/Pharmacodynamic
PopPK, Population Pharmacokinetics
QSAR, Quantitative structure activity relationship
QSP, Quantitative systems pharmacology
QSPR, Quantitative structure-property relationship
MBMA, Model-based meta-analysis
AI/ML, Artificial intelligence / machine learning

Courtesy by Dr. Kimberly Bergman
Avenues for Regulatory Interaction

- To enhance interactions among stakeholders in new drug development
- To support efficient drug development and rationale decision-making
MIDD Paired Meeting Program

Objectives:
• To promote early interaction between drug developers and the agency on key issues in a specific development program.
• To enhance collaboration among all stakeholders in new drug development.

Regulatory Tool
- MIDD guidance
- MIDD related public workshops
- MIDD related SOPs

• Initiated from PDUFA 6 discussion.
• Jointly administered by CDER and CBER
• Products should be registered under U.S. INDs, NDAs, or BLAs
• Submissions are accepted on a continuous basis
• The selection committee meets on a quarterly basis.
History and Future of the MIDD Program

04/16/2018: FDA announced the availability of the MIDD pilot review program.

07/2018: FDA granted the first MIDD request.

06/15/2022: The pilot review program is expected to accept submissions until June 2022.

Q1 FY2023: FR Notice: Continuation of the MIDD paired meeting program

PDUFA VI: MIDD Paired Meeting Pilot Program

PDUFA VII: MIDD Paired Meeting Program
MIDD Paired Meeting Overview

**Courtesy: Dr. Kimberly Bergman**

**MIDD Paired Meeting Overview**

**2nd Meeting: 60 days after receiving the meeting package**

**INTERNAL MEETINGS**

**INITIAL SPONSOR MEETING**

**INTERNAL MEETINGS**

**FOLLOW-UP SPONSOR MEETING**

**COMMUNICATIONS**

**FORMAL COMMUNICATIONS**

(PRELIMINARY COMMENTS AND MINUTES)

**INPUT FROM OCP-LED MULTIDISCIPLINARY TEAM**

**QUARTERLY**

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**MIDD SELECTION COMMITTEE MEETING**

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Impact on Drug Development

To inform trial design and patient selection

To improve dose selection, optimization and risk mitigation

To enhance therapeutic individualization

To support approval of new dose, dosing regimen, formulation, etc.
Case Examples
Semaglutide (OZEMPIC®)

- A glucagon-like peptide 1 (GLP-1) receptor agonist.
- Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Chemical Structure of Semaglutide

Limitations of Use:
- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.
- Has not been studied in patients with a history of pancreatitis. Consider another antidiabetic therapy.
- Not indicated for use in type 1 diabetes mellitus or treatment of diabetic ketoacidosis.

* Semaglutide Label: << Drugs@FDA: FDA-Approved Drugs>>
Administer OZEMPIC subcutaneously to the abdomen, thigh, or upper arm. Instruct patients to use a different injection site each week when injecting in the same body region.

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**Approved Dosing:**
- Start with 0.25 mg Q weekly for 4 doses.
- Increase dose to 0.5 mg Q weekly.
- Initially, the maximum dose is 1 mg Q weekly.
- Now the maximum dose is increased to 2 mg Q weekly.

* Semaglutide Label: << Drugs@FDA: FDA-Approved Drugs >>
# Initial Clinical Trial

<table>
<thead>
<tr>
<th>30 Weeks</th>
<th>1 mg Arm</th>
<th>0.5 mg Arm</th>
<th>Placebo Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HbA1C*</td>
<td>FPG*</td>
<td>Baseline BMI</td>
</tr>
<tr>
<td></td>
<td>-1.6</td>
<td>-44</td>
<td>34.0</td>
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<td>-1.4</td>
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<td>-0.1</td>
<td>-15</td>
<td>32.5</td>
</tr>
</tbody>
</table>

- **30 Weeks**
- **HbA1C***: Change from baseline @ Week 30
- **FPG***: Change from baseline @ Week 30
- **Baseline BMI**: Baseline body mass index
- **Baseline BW***: Baseline body weight
- **BW***: Change from baseline @ Week 30
- **Per HbA1C < 7%***: Percentage of patients with HbA1C < 7%

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1. The average body weight in T2D patients is high
2. There is still room for improvement following the treatment of 1 mg dosing (*20-30% of pats failed to achieve the treatment target*).
Suggestions from MIDD Analysis

**Population PK Analysis**

- One-compartment model with first-order absorption and elimination
- Body weight has been identified as the main covariate for exposure: \( CL \sim f(BW, \text{Age, Race, Gender, Ethnicity...}) \).
- Exposure in patients with higher body weight tends to be lower.

\[
Effect_{BW} = \left(\frac{BW}{85}\right)^\theta
\]

OCP review: <<<Ozempic (semaglutide) Injection (fda.gov)>>
Better Improvement on efficacy (HbA1C, Body weight, etc) is anticipated with increased semaglutide exposure
Subsequent Clinical Trial

**40 Weeks**

| 1 mg Arm | 2 mg Arm |

~ 900 T2D pts

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**Mean HbA1C**

-0.23,

P=0.0003

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**Mean Body Weight**

-0.93,

P=0.015

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**: Treatment Difference, baseline-adjusted**

1. ClinicalTrials.gov <<A Research Study to Compare Two Doses of Semaglutide Taken Once Weekly in People With Type 2 Diabetes - Study Results - ClinicalTrials.gov>>

2. Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial. doi: 10.1016/S2213-8587(21)00174-1. Epub 2021 Jul 21
Clinical Trials to Support Initial Approval

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* Semaglutide Label: << Drugs@FDA: FDA-Approved Drugs>>
Take-Home Messages

• To select appropriate treatment and dosing for obese patients is important in new drug development

• MIDD, as a technical and regulatory tool, may be used to facilitate new drug development in obese patient population.
Acknowledgement

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- Shiew-Mei Huang

- Issam Zineh
Questions or Comments?

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