U.S. FOOD & DRUG ADMINISTRATION

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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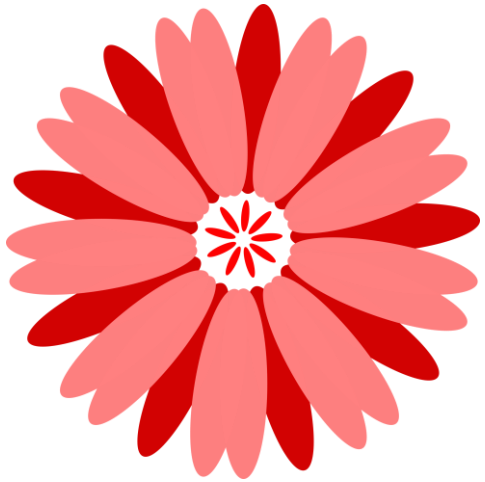
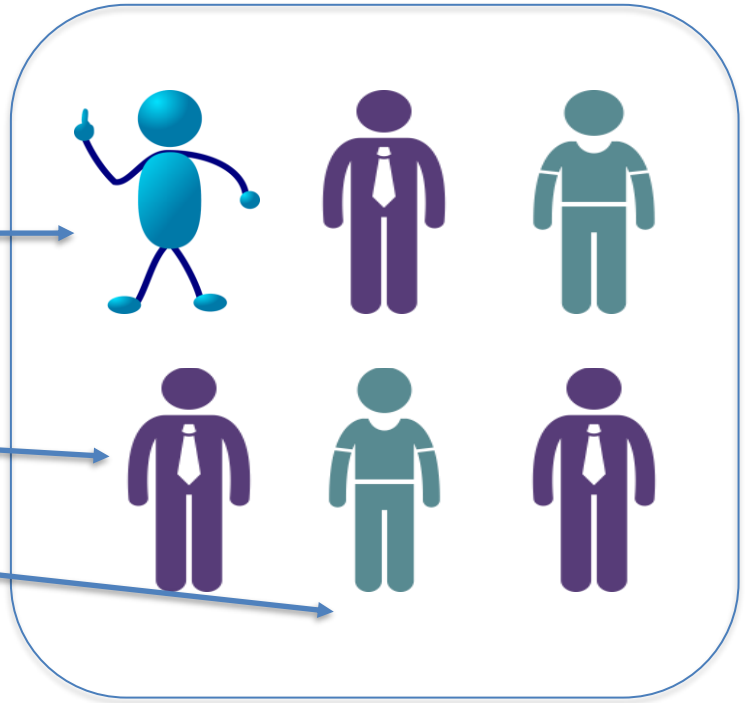
Outline

- 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

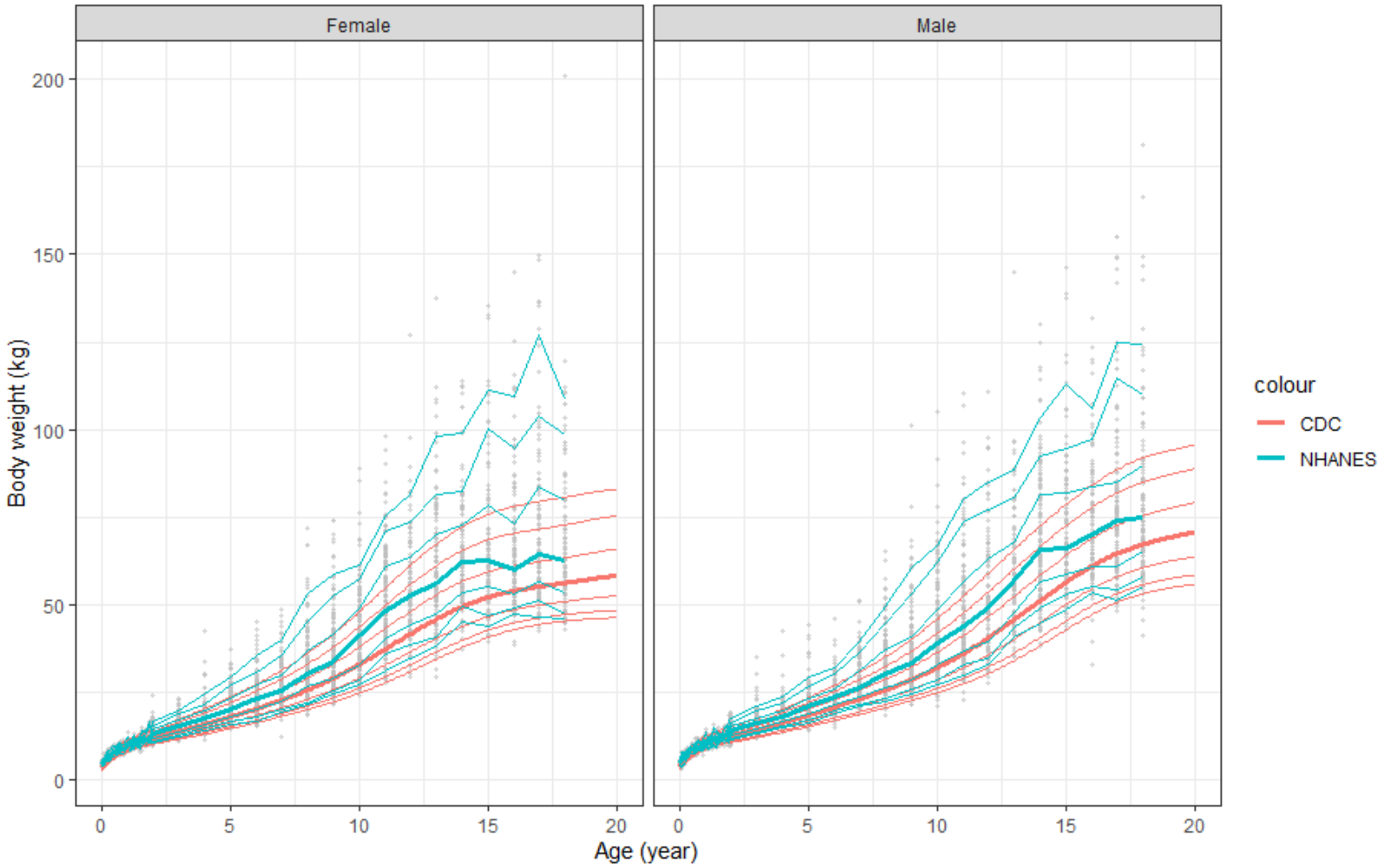
Intrinsic Factors:
(Permanent Difference)

- 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

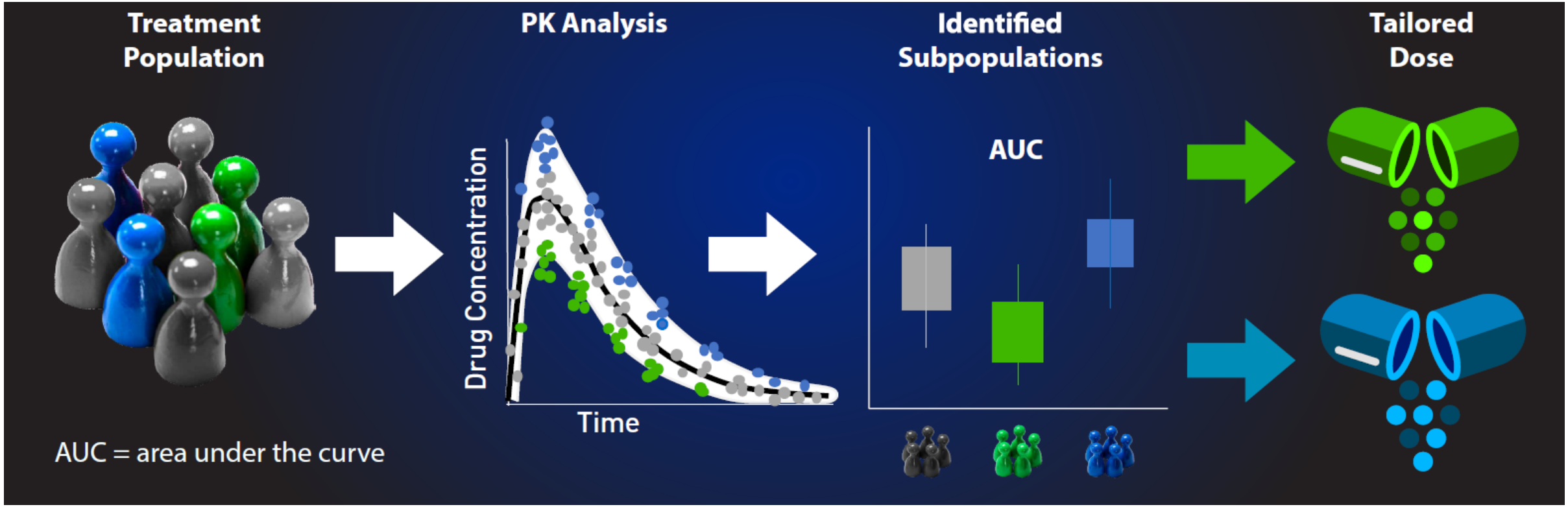
Type 2 Diabetes

- 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.

Body Weight and Pharmacology



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.

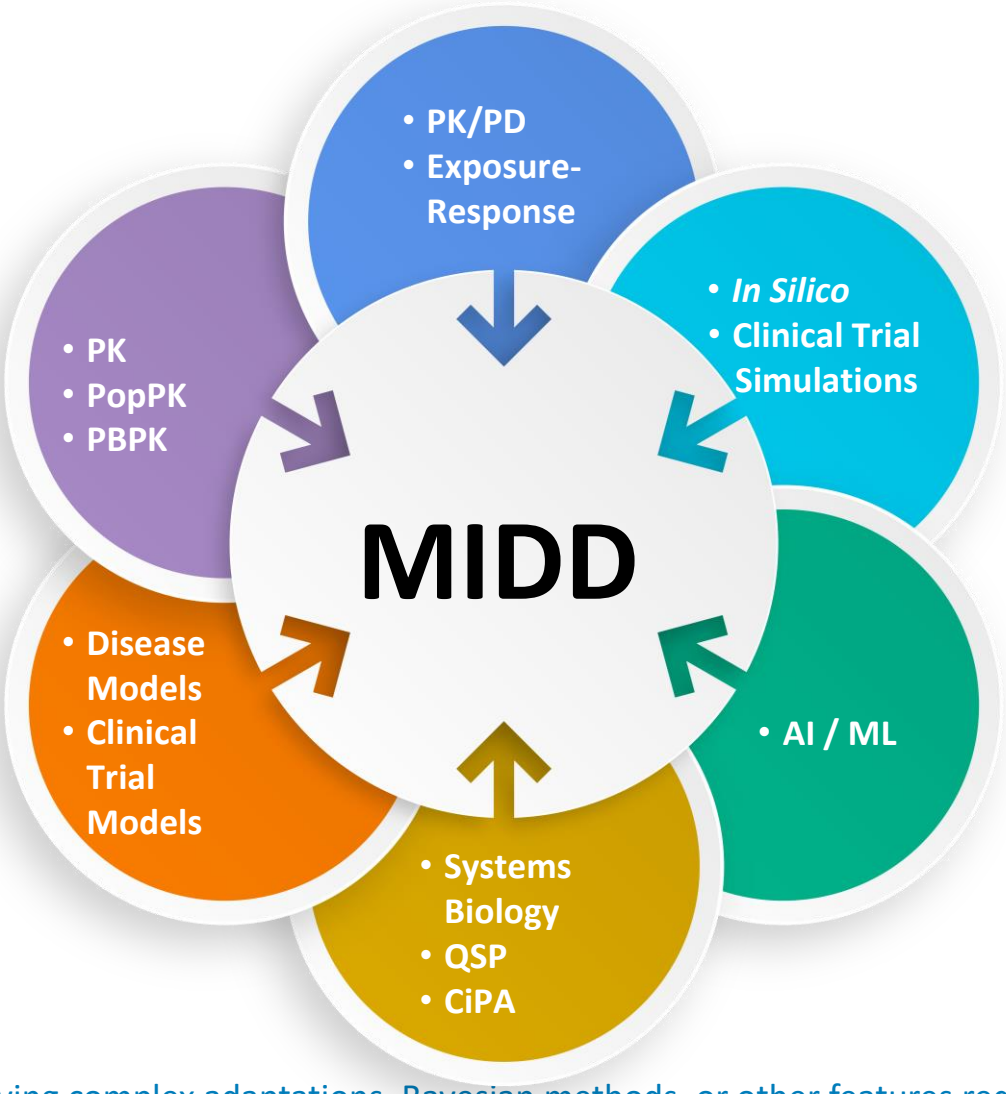
Regulatory Tool:

To promote early interaction between the drug developers and FDA on key issues.

(MIDD Paired Meeting Program)

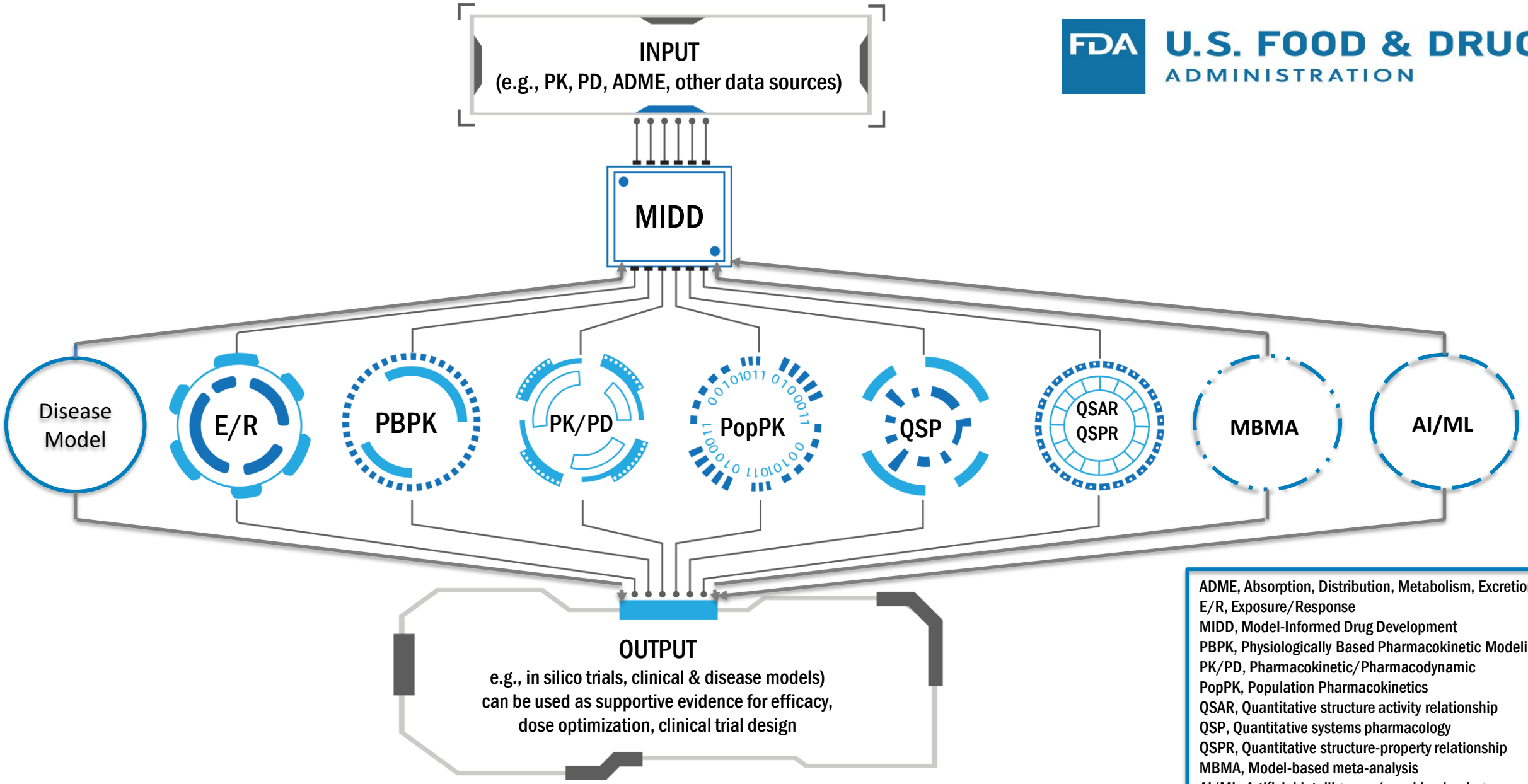
Model-Informed Drug Development

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



To Support appropriate usage of a drug in a specific population

* 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.

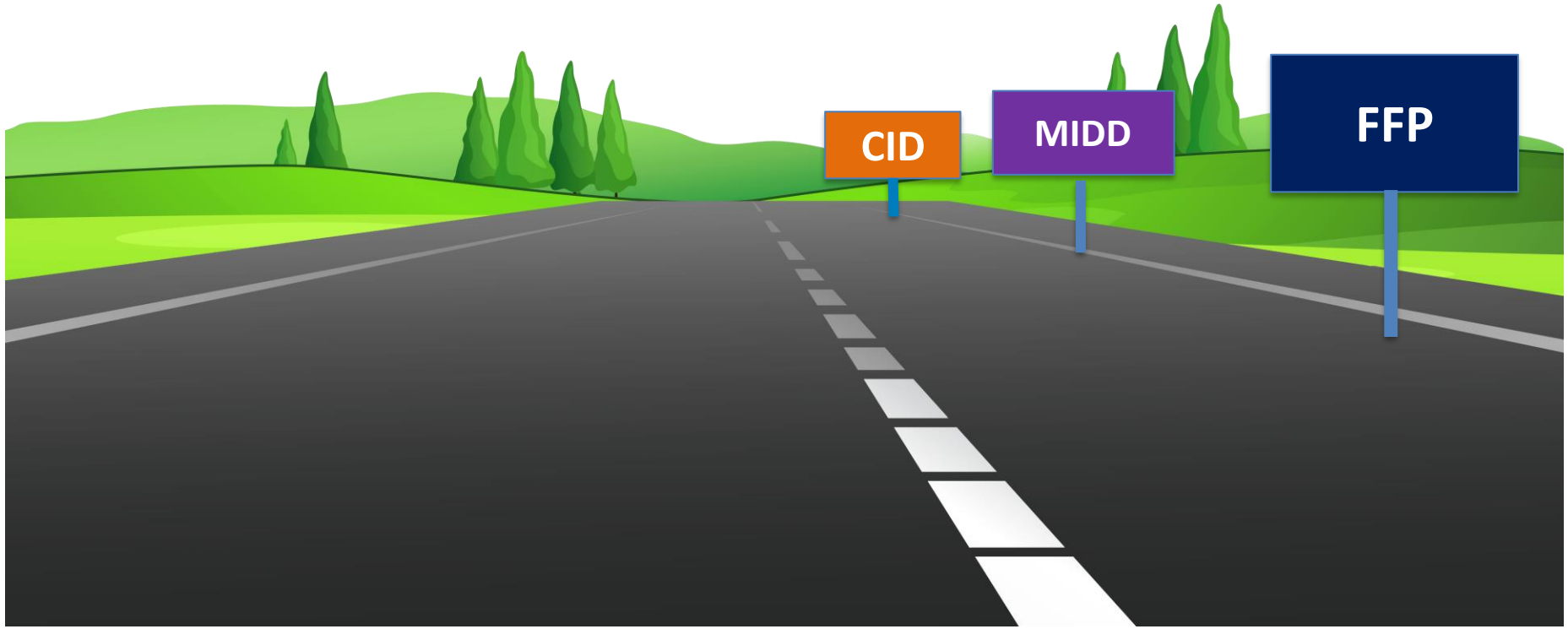


FDA U.S. FOOD & DRUG ADMINISTRATION

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 learing

Courtesy by Dr. Kimberly Bergman

Avenues for Regulatory Interaction



- To enhance interactions among stake holders in new drug development
- To support efficient drug development and rationale decision-makring

MIDD Paired Meeting Program

- 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.

Regulatory Tool

Objectives:

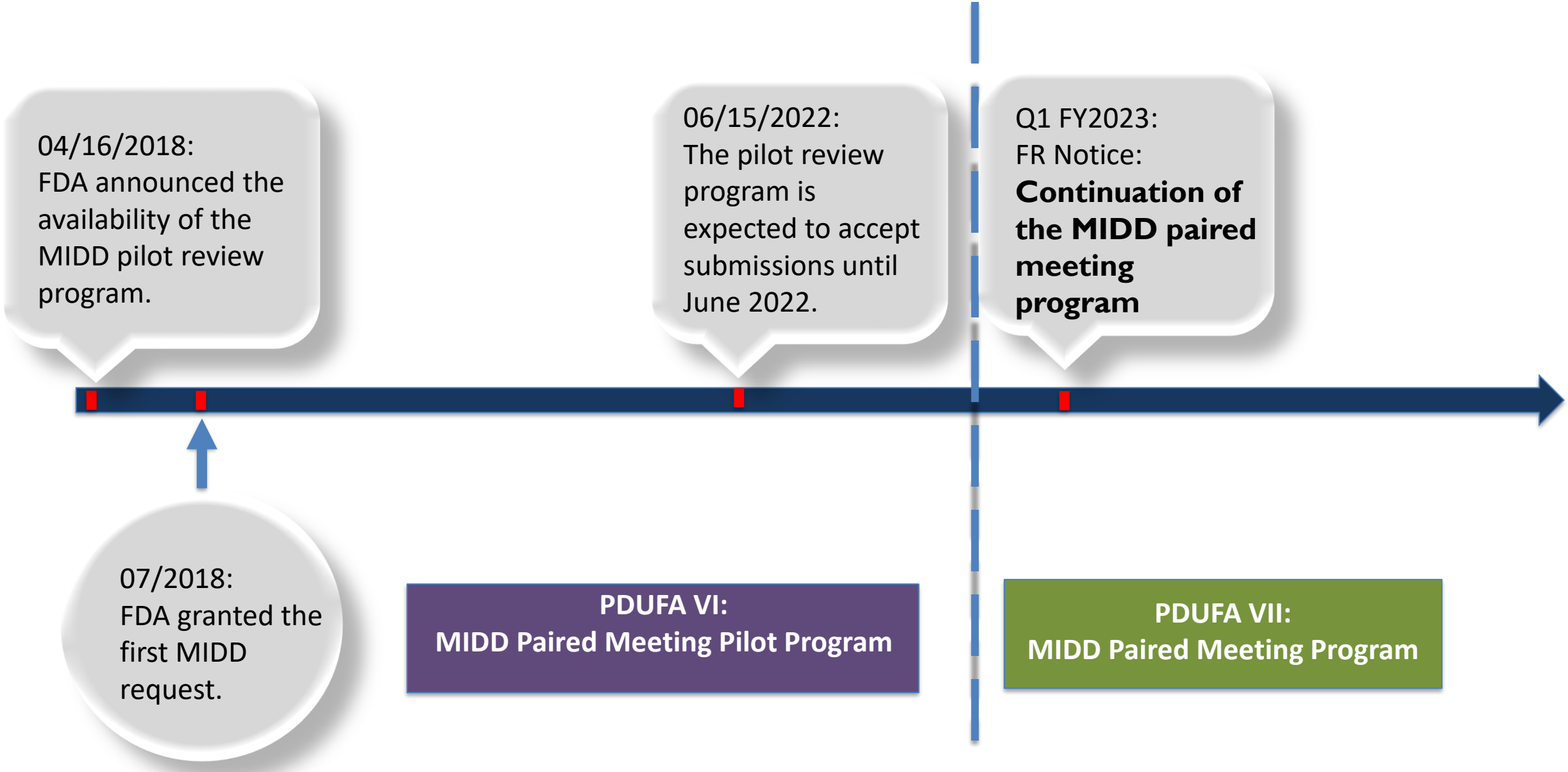
- To promote early interaction between drug developers and the agency on key issues in a specific development program.
- To enhance collaboration among all stake holders in new drug development.

MIDD guidance

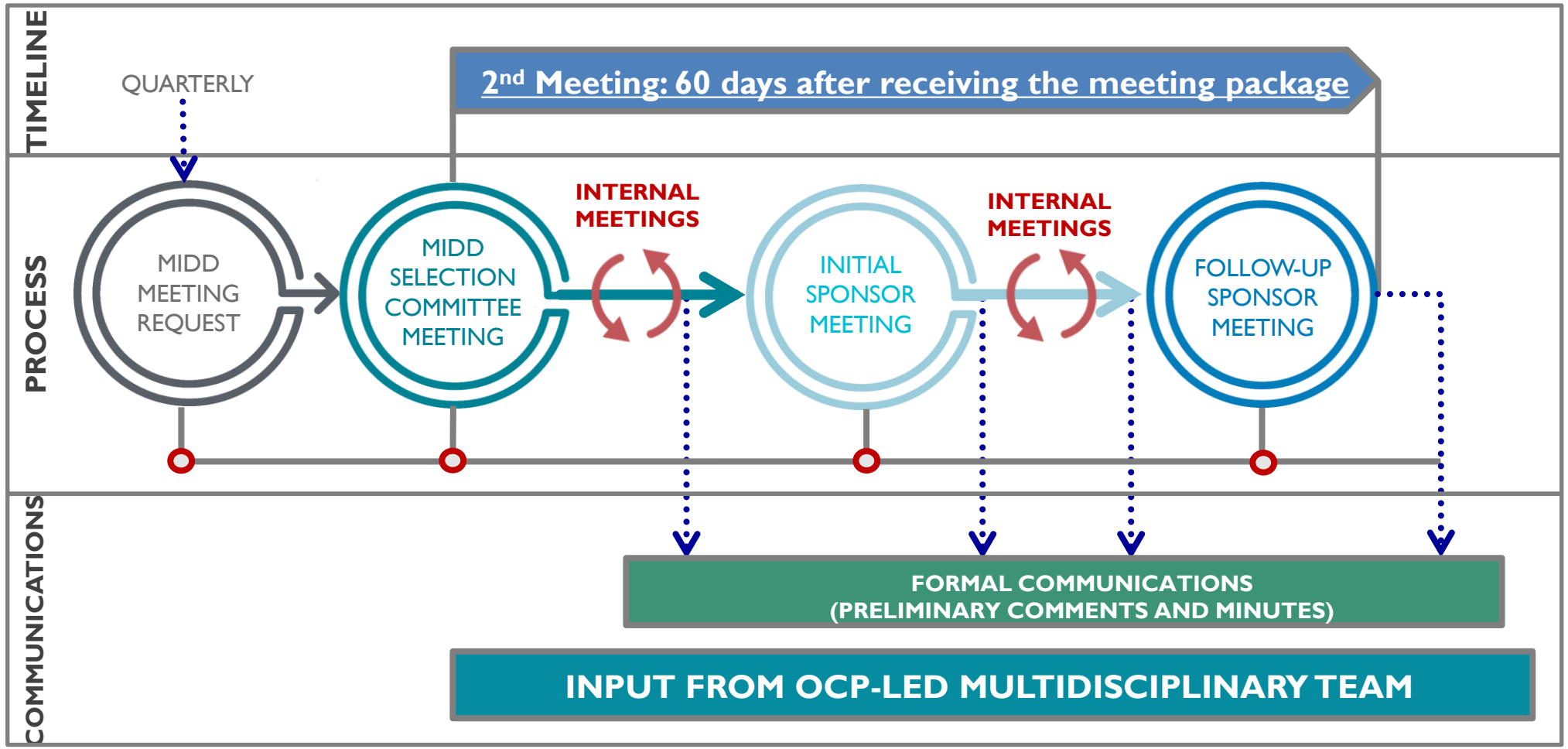
MIDD related public workshops

MIDD related SOPs

History and Future of the MIDD Program



MIDD Paired Meeting Overview



Courtesy: Dr. Kimberly Bergman

Impact on Drug Development

To inform trial design and patient selection

To improve dose selection, optimization and risk mitigation

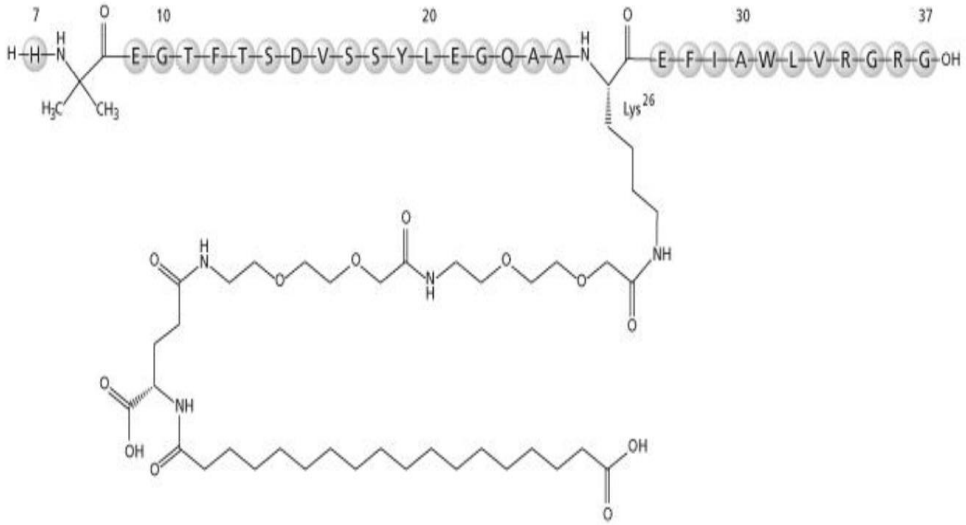
To enhance therapeutic individualization

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

- A GLP-1 analogue with 94% sequence homology to human GLP-1.
- GLP-1 is a physiological hormone that has multiple actions on glucose, mediated by the GLP-1 receptors.
- Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner.

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>>

Clinical Trials to Support Initial Approval

Dose per Injection	Total Strength per Total Volume	Strength per mL
0.25 mg 0.5 mg	2 mg / 3 mL	0.68 mg/mL
0.25 mg 0.5 mg	2 mg / 1.5 mL	1.34 mg/mL
1 mg	4 mg / 3 mL	1.34 mg/mL

- 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

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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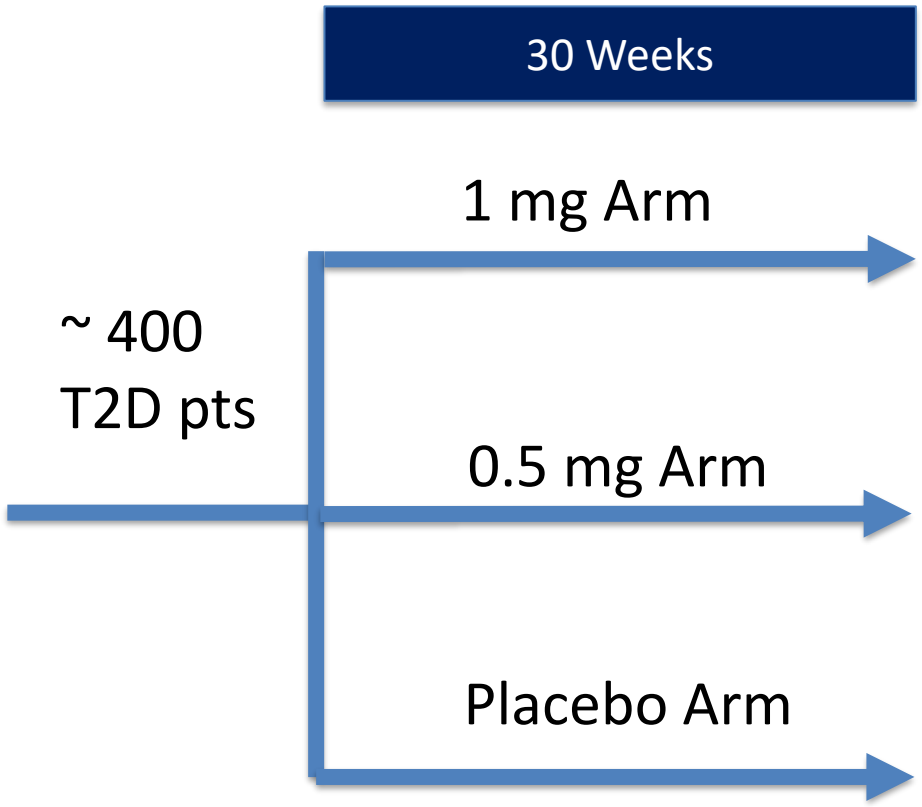
Initial Clinical Trial



30 Weeks	HbA1C*	FPG*	Baseline BMI	Baseline BW*	BW*	Per HbA1C < 7%*
1 mg Arm	-1.6	-44	34.0	96.9	-4.7	70
0.5 mg Arm	-1.4	-41	32.5	89.8	-3.8	73
Placebo Arm	-0.1	-15	32.5	89.1	-1.2	28

*: Change from baseline @ Week 30

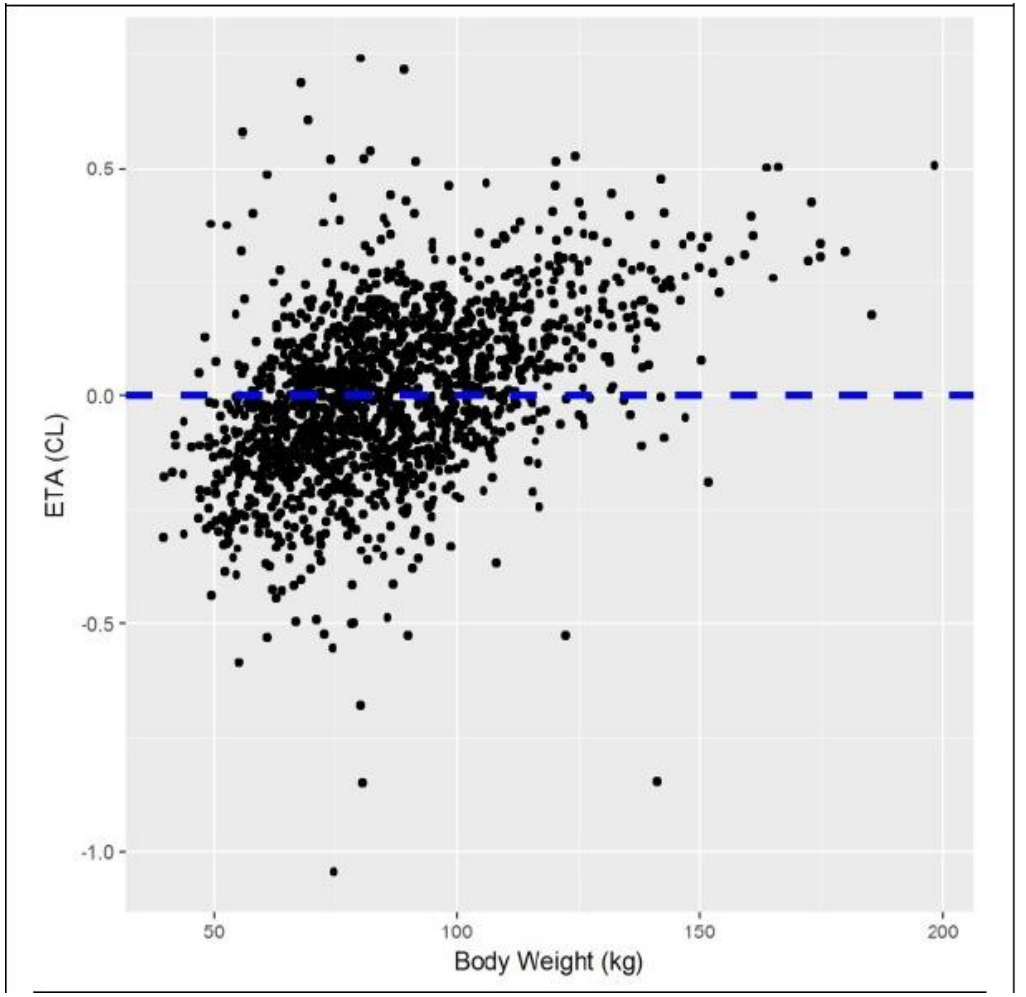
1. The average body weight in T2D patients is high
2. There is still room for improvement following the treatment of 1 mg dosing (**20-30% of pats failed to achieve the treatment target**).

Suggestions from MIDD Analysis

Population PK Analysis

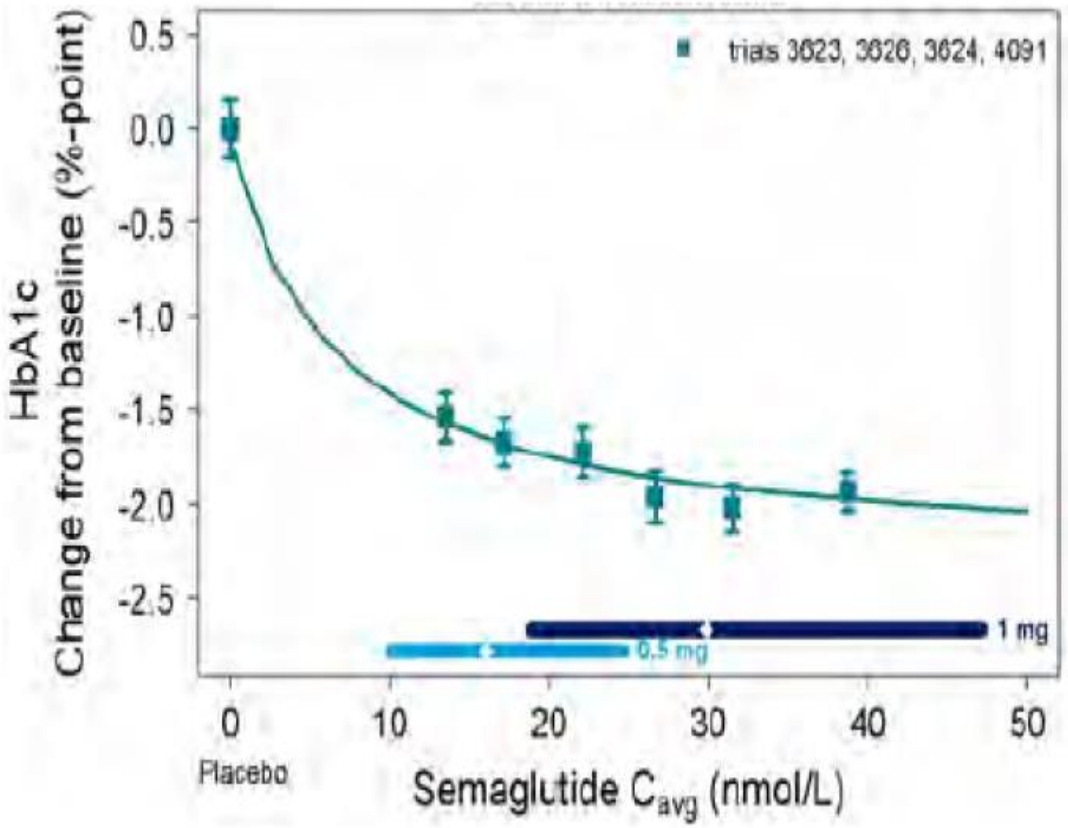
- One-compartment model with first-order absorption and elimination
- Body weight has been identified as the main covariate for exposure: CL ~ f(***BW***, Age, Race, Gender, Ethnicity…).
- Exposure in patients with higher body weight tends to be lower.

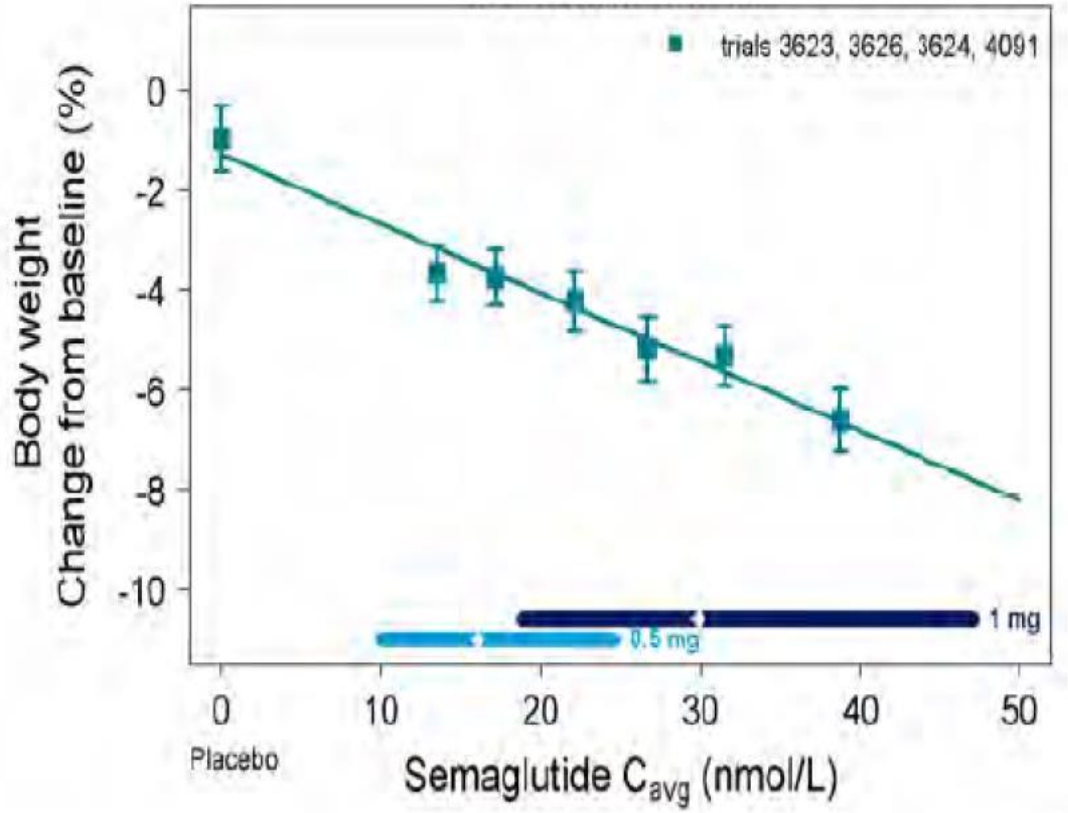
$$Eeffect_{BW} = (\frac{BW}{85})^{\theta}$$



OCP review: <<Ozempic (semaglutide) Injection (fda.gov)>>

Exposure-Response Analysis





Better Improvement on efficacy (HbA1C, Body weight, etc) is anticipated with increased semaglutide exposure

OCP review: <<Ozempic (semaglutide) Injection (fda.gov)>>

Subsequent Clinical Trial

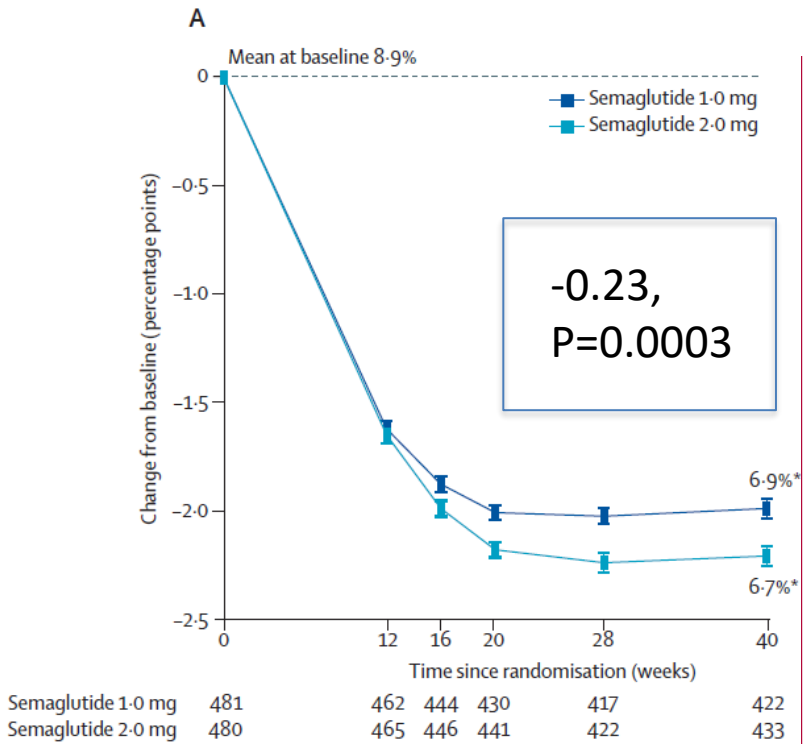
40 Weeks

~ 900
T2D pts

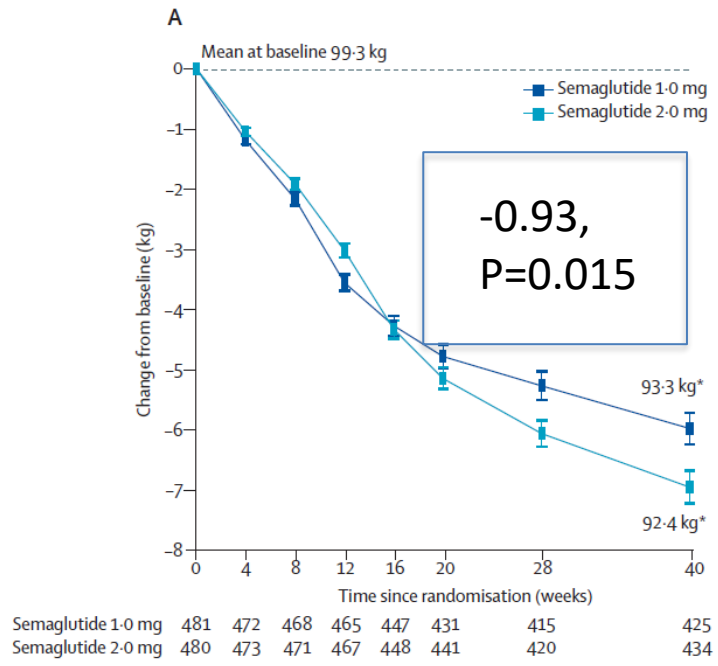
2 mg Arm

1 mg Arm

Mean HbA1C



Mean Body Weight



**: 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

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2 mg	8 mg / 3 mL	2.68 mg/mL

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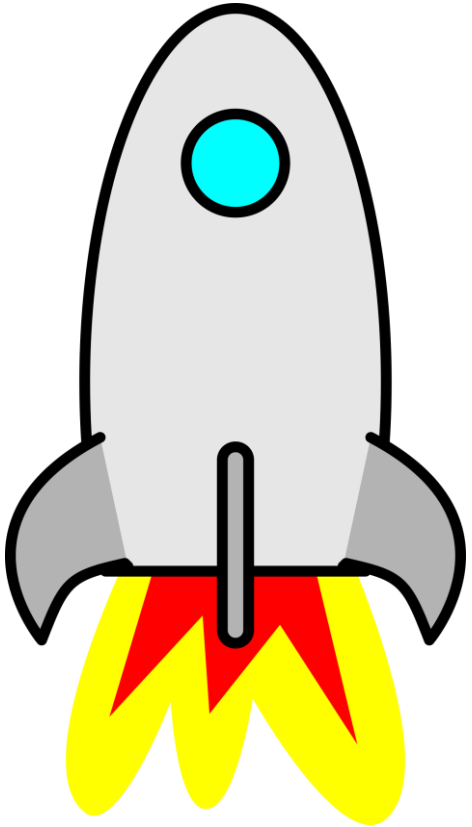
Take-Home Messages

- 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

- Dr. Xiaolei Pan
- Dr. Ye Xiong
- Dr. Justin Earp
- Dr. Vasha Mehta
- Dr. Gil Burkcark
- Semaglutide review team
- DPM members
- OCP Members
- Shiew-Mei Huang
- Issam Zineh

Questions or Comments ?

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