Clinical Trials Protocol on Oral Tirzepatide

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Introduction

- Type 2 diabetes (T2DM), a metabolic disorder associated with impaired glucose homeostasis, affects approximately 30 million people in the United States (US), and accounts for 90-95% of all diabetes mellitus cases. (NDA 215866)

- **Diabetes Diagnosis (ADA):**
    - HbA1c: 6.5% or higher
    - Fasting Plasma Glucose (FPG): 126 mg/dL or higher
    - Oral Glucose Tolerance Test (OGTT): 200 mg/dL or higher
    - Random Plasma Glucose Test: 200 mg/dL or higher

Diabetes Treatments

- There are currently 12 pharmacologic classes of diabetes medications approved for the treatment of type 2 diabetes mellitus including GLP-1 receptor agonists.

- Common classes:
  - Metformin
  - Dipeptidyl peptidase 4 (DPP-4) inhibitors
  - Glucagon-like peptide 1 (GLP-1) and dual GLP-1/gastric inhibitory peptide (GIP) receptor agonists
  - Sodium-glucose cotransporter 2 (SGLT2) inhibitors
  - Sulfonylureas
  - Thiazolidinediones (TZDs)

Current Popular GLP-1 Treatment on the Market

Generic Name	Brand Name	Producer	Year of Approval	Doses Forms and Strength
Semaglutide(Oral)	Rybelsus	Novo Nordisk	2019	3mg, 7mg and 14mg
Semaglutide(Injectable)	Ozempic	Novo Nordisk	2017	0.25mg, 0.5mg, 1mg or 2mg per 1.5ml
Tirzepatide(Injectable)	Mounjaro	Eli Lilly	2022	2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL

- Injectable semaglutide or tirzepatide are taken once a week
- Oral semaglutide is taken once a day.

Brief Introduction of IND

- Oral Tirzepatide (co-formulated with an absorption enhancer sodium)
- Improve glycemic control in adults with T2DM

Objective and Endpoints of Phase I

Primary Objective	**To investigate the safety and tolerability by single and multiple doses of oral tirzepatide to healthy subjects and patients with T2DM**	• Adverse event and safety glucose monitoring
Secondary Objectives	• **To characterize the PK of oral tirzepatide to healty subjects and patients with T2DM** • **To investigate the PD effects of multiple doses to healthy subjects** • **To investigate the PD effects of multiple doses to patients with T2DM**	• Blood sample will be evaluated for tirzepatide concentration • Glycemic control(fasting, Oral glucose tolerance), weight, lipids • Glycemic control(fasting, Oral glucose tolerance, HbA1c), weight, lipids
Exploratory Objective	**TBD**	• TBD

Highlight of inclusive/exclusive criteria in phase I

Part A: SAD

HV
Single Dose
6-week

- 18-50 years old adults
- BMI 18.5–27.5 kg/m²

Part B: MAD

HV
Multiple Doses
4-week

- 18-64 years old adults
- BMI 20.0–29.9 kg/m²

Part C: T2DM

T2DM
Multiple Doses
4-week

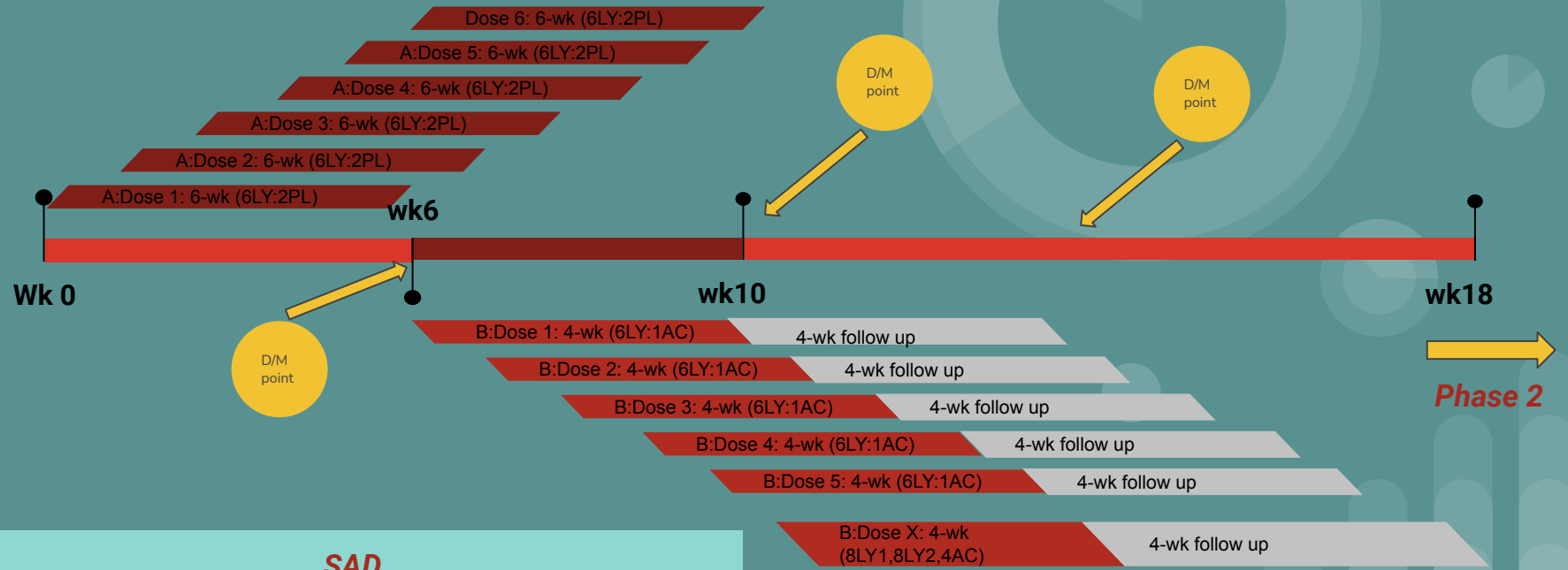
- Diagnosis < 10yrs
- 18-64 years old adults
- HbA1c of 6.5–9.0%
- BMI of 20.0–37.0 kg/m²

Overall Design of Phase I

Multiple-site, double-blind, placebo-controlled, randomized, parallel-dose group
14-week + 4-week follow up

MAD

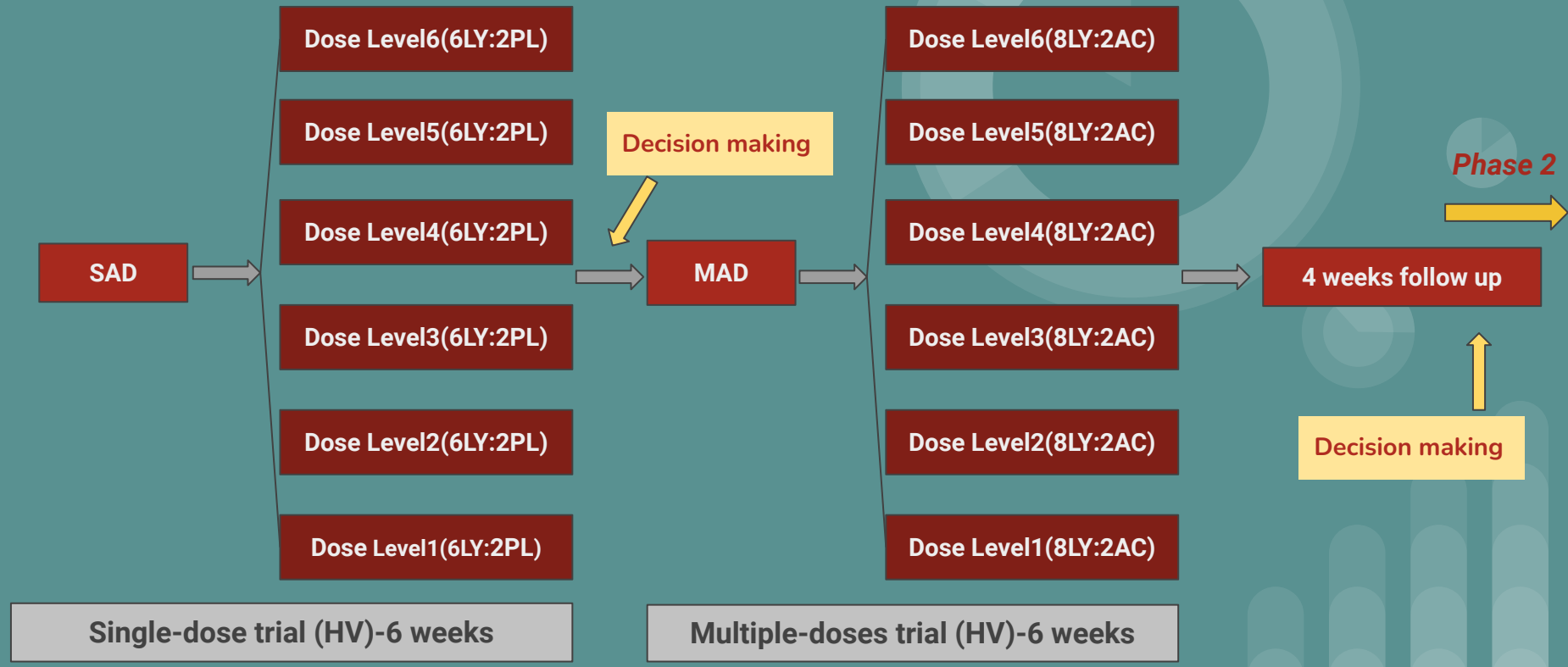
Dose range: Dose 1(lowest)~Dose 6(highest)
N = 55
AC:Metformin



SAD

Dose range: Dose 1(lowest)~Dose 6(highest)
N = 48

Overall Design of Phase I (option 2)



How do competitors perform on clinical endpoints?

	Semaglutide (Oral)	Semaglutide (SC)	Tirzepatide (SC)
mean change in HbA1c	-0.6 (3mg) to -1.4 (14mg)	-1.6 (1mg)	-1 (1mg) to -2 (15mg)
mean change in body weight (kg)	-0.9 (3mg) to -3.7 (14mg)	-4.7 (1mg)	-1 (1mg) to -11 (15mg)

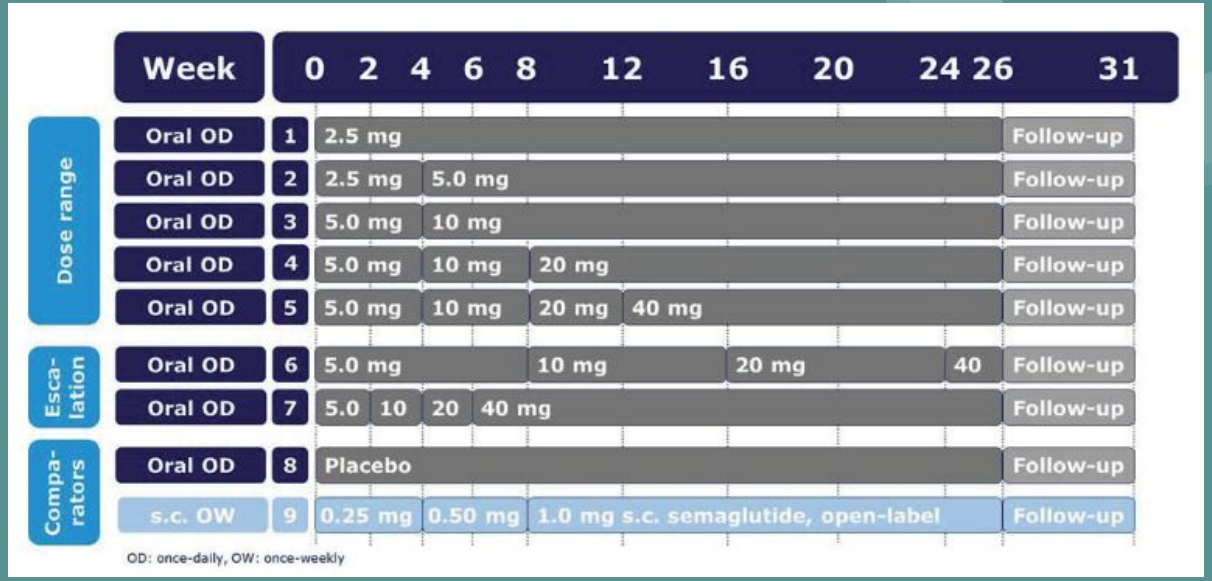
Phase II

- Primary questions:
  - Does oral tirzepatide help manage T2DM and help with weight loss?
  - Which doses best balance efficacy and safety?
- Endpoints:
  - mean change in HbA1C
  - mean change in body weight
- Used as add-on with metformin
- Duration: 26 weeks
- Advance to Phase 3 if
  - mean change HbA1C <= -0.6(%)
  - mean change weight <= -1(kg)
- Patient population:
  - Type 2 diabetes patients
  - HbA1c between 7% and 10%
  - T2DM controlled with diet and exercise alone or are stable on metformin for at least 60 days
  - BMI >= 25

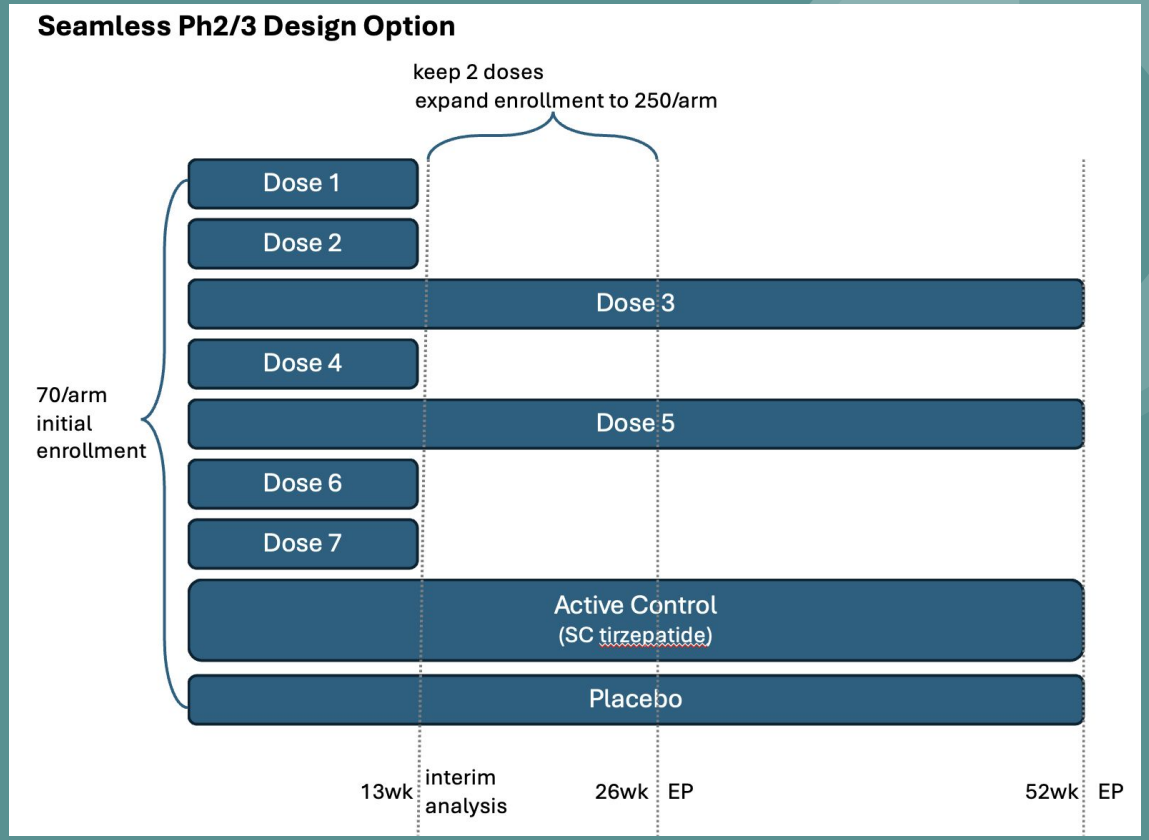
	Option 1	Option 2	Option 3
Basic Design	POC then DF POC: 2 doses DF: 4 oral doses 1 placebo	Simultaneous POC + DF 7 oral doses 1 SC tirzepatide 1 placebo	Seamless Ph2-3 7 initial doses, keep 2 after 26wk EP 1 SC tirzepatide 1 oral semaglutide
Sample size	70/arm	700	70/arm initially, expand to 250/arm for 2 doses + AC + placebo after 26wk EP
Pros/Cons	if POC looks bad, can end study before DF slower than other options	quicker to Ph3 higher upfront cost/risk than Option 1	smaller sample size for Ph2/Ph3 potentially faster logistically difficult
Other			continue 2 doses + AC + placebo until 52wk EP

Example: Simultaneous POC+DF (Option 2)

(Novo Nordisk semaglutide tablet Phase 2 design)



Seamless Ph2/3 (Option 3)



Phase III

- Primary question:
  - Investigate the efficacy, safety, and tolerability of oral trizepitide added to metformin.
- Primary endpoint:
  - Change in HbA1c
- Secondary Endpoints:
  - Change in 2 hour plasma glucose,
  - Change is body weight, and
  - Change in fasting plasma glucose.
- Duration: 26/52 weeks
- Patient population:
  - Type 2 diabetes patient
  - HbA1c between 7% and 10%
  - T2DM controlled with diet and exercise alone or are stable on metformin for at least 60 days
  - BMI >= 25

	Option 1	Option 2	Option 3
Basic design	simultaneous 3 treatment arms + placebo	simultaneous 3 treatment arms + placebo with interum analysis	Seamless Ph2/3
Sample size	700 randomized to about 175 per arm	700	Smaller
Cosiderations	Treatment Dosages	Interum analysis at 26 weeks Cost	FDA may require larger safety database