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	Mean Change in HbA1c (%)	Mean Change in Body Weight (kg)
Semaglutide (Oral)	Rybelsus	Novo Nordisk	2019	3, 7, 14 mg	-0.6 (3mg) to -1.4 (14mg) (vs placebo)	-0.9 (3mg) to -3.7 (14mg)
Semaglutide (Injectable)	Ozempic	Novo Nordisk	2017	0.25, 0.5, 1, 2 mg/1.5ml	-1.4 (0.5mg) to -1.6 (1mg) (vs placebo)	-3.7 (0.5mg) to -4.7 (1mg)
Tirzepatide (Injectable)	Mounjaro	Eli Lilly	2022	2.5, 5, 7.5, 10, 12.5, 15 mg/0.5 mL	-1 (1mg) to -2 (15mg) (vs placebo)	-1 (1mg) to -11 (15mg)

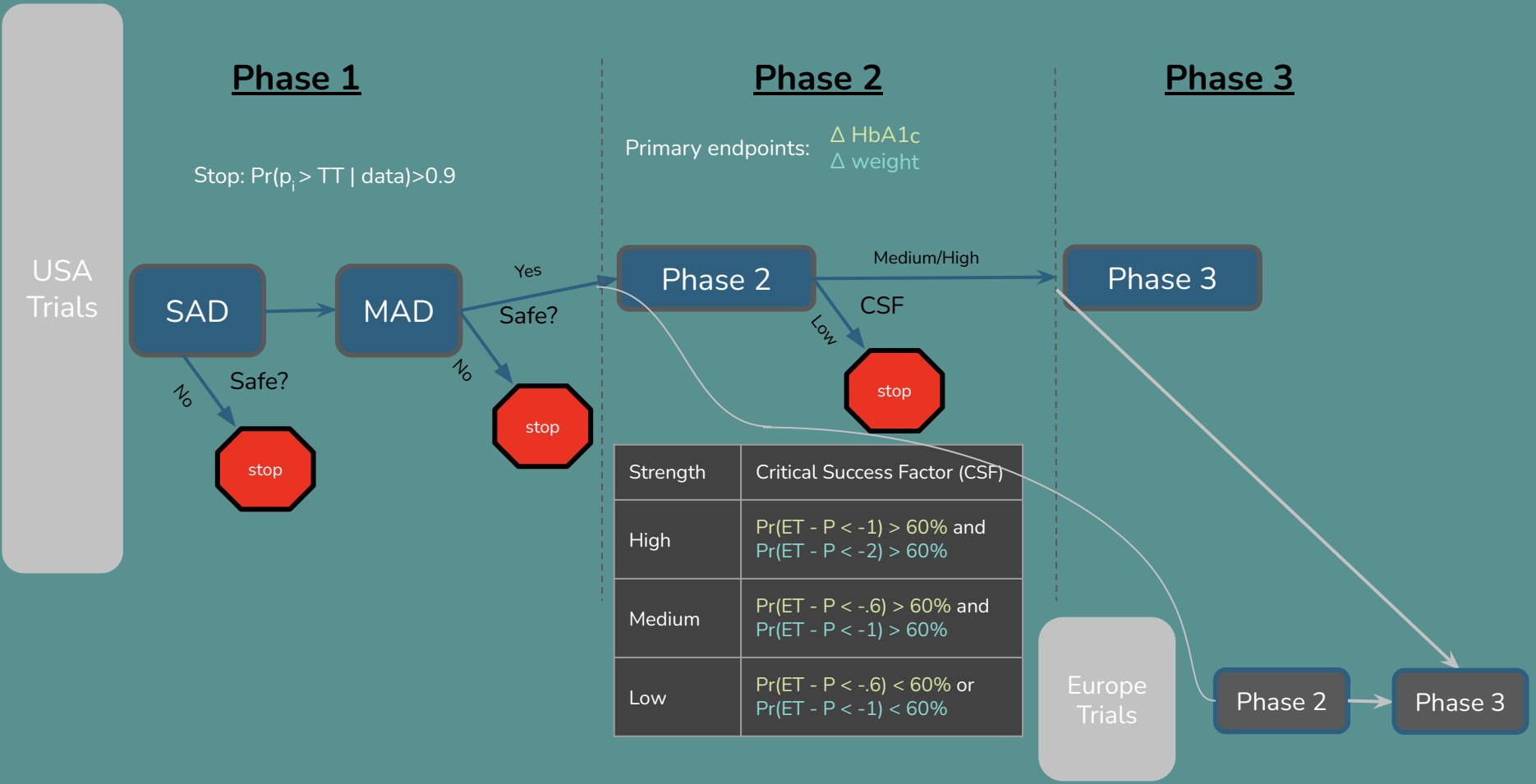
- Injectable semaglutide or tirzepatide are taken once a week
- Oral semaglutide is taken once a day.

Proposed Treatment

- Oral Tirzepatide (co-formulated with an absorption enhancer sodium)
  - Improve blood glucose control in adults with T2DM
  - Provide substantial weight loss benefits

Small Molecule (Daily, Fasting)
Fast Active
Less Side Effects

Trial Plan Overview

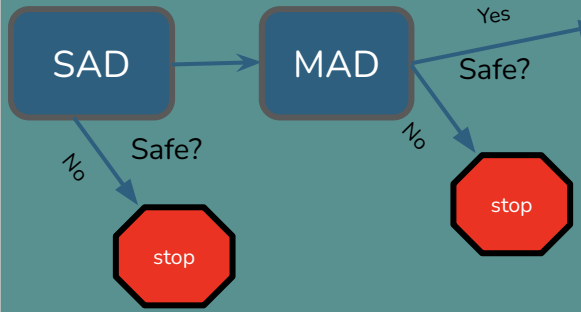


Trial Plan Overview

USA Trials

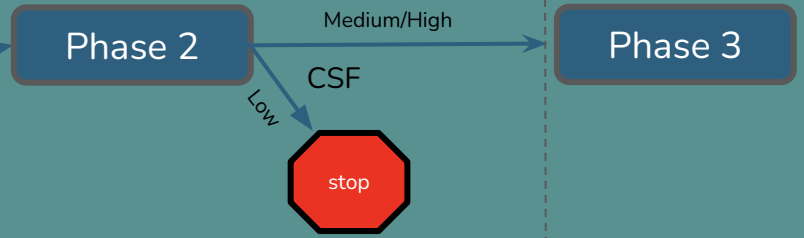
Phase 1

Stop: $Pr(p_i > TT \mid data) > 0.9$



Phase 2

Primary endpoints: Δ HbA1c, Δ weight



Strength	CSF Criteria
High	Pr(ET - P < -1) > 60% and Pr(ET - P < -2) > 60%
Medium	Pr(ET - P < -.6) > 60% and Pr(ET - P < -1) > 60%
Low	Pr(ET - P < -.6) < 60% or Pr(ET - P < -1) < 60%

Phase 3

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	• Blood sample will be evaluated for tirzepatide concentration
	• To investigate the PD effects of multiple doses to healthy subjects	• Glycemic control(fasting, Oral glucose tolerance), weight, lipids
	• To investigate the PD effects of multiple doses to patients with T2DM	• 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

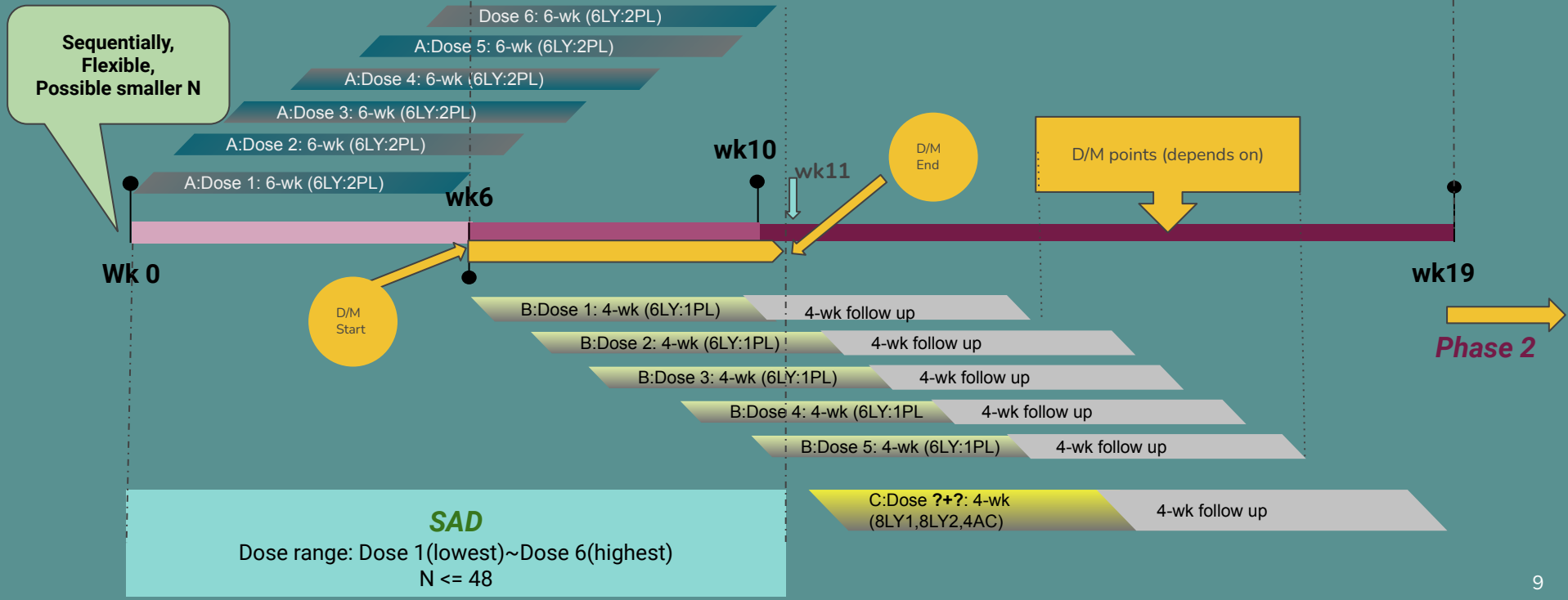
- Diagnosis < 10yrs
- 18-64 years old adults
- HbA1c of 6.5–9.0%
- BMI of 20.0–37.0 kg/m²

Overall Design of Phase I

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

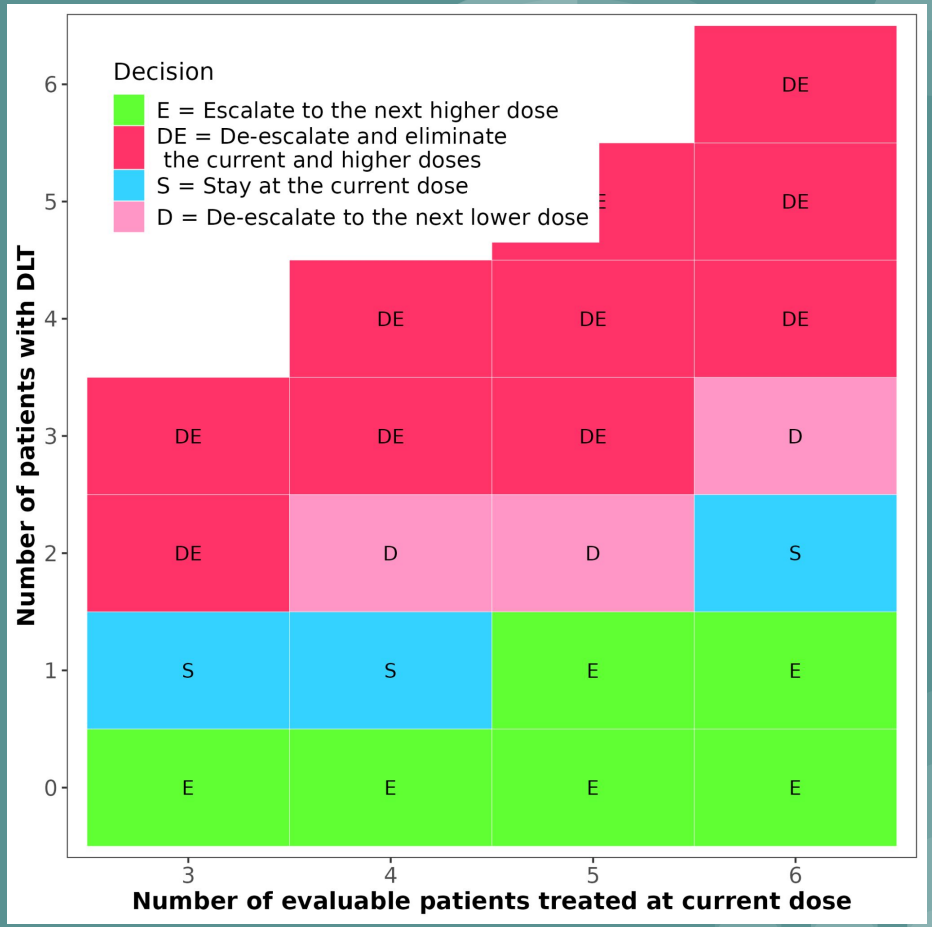
$Pr(p_i|data)$: 25 ~50 ~70 Rule
Es: $Pr_e < 0.25$
DeEs: $Pr_d > 0.50$

MAD
Dose range: Dose 1(lowest)~Dose 6(highest), N = 55 ~ 63 (depends on)
Dose escalation 2~3wks, maintenance 5~6wks



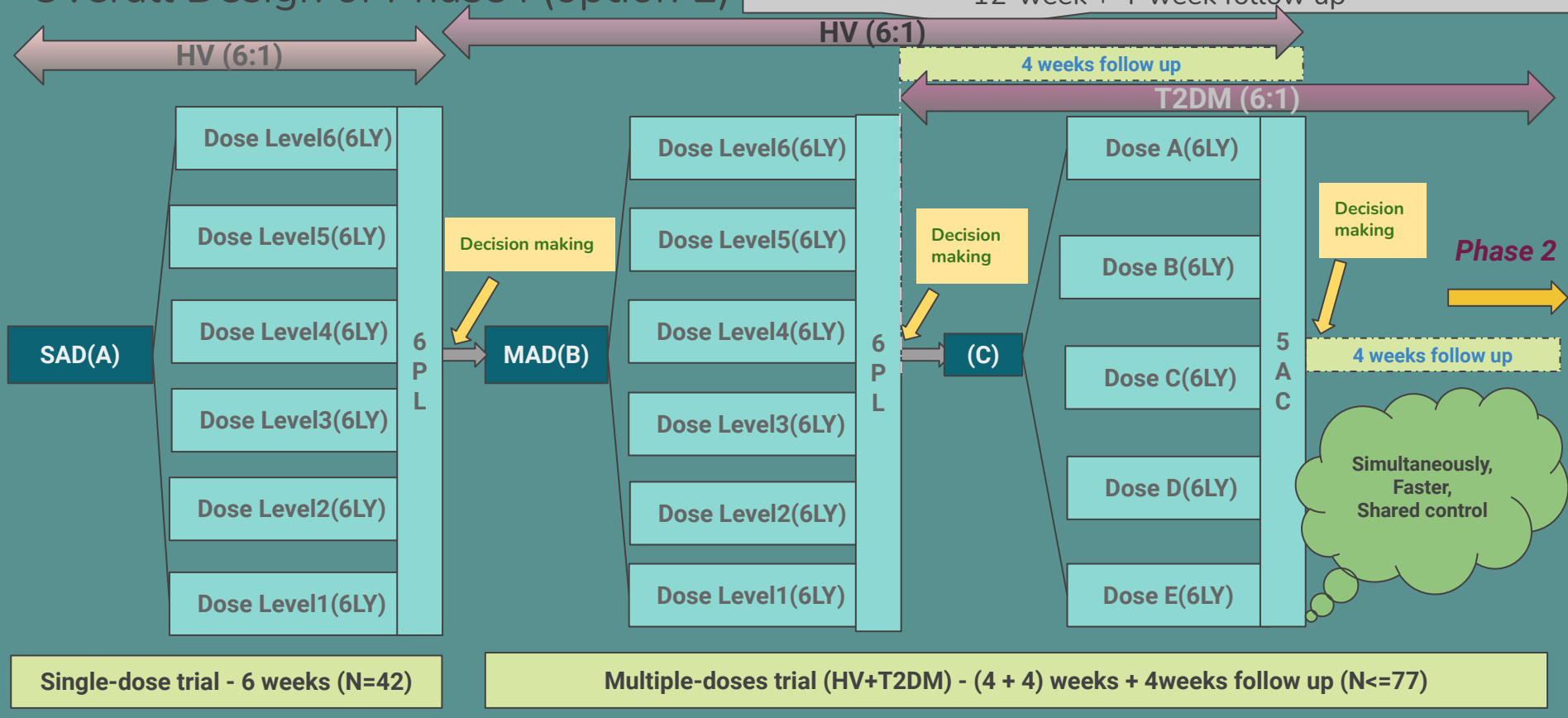
SAD
Dose range: Dose 1(lowest)~Dose 6(highest)
N <= 48

Decision Table for Dose Escalation and De-escalation (w/ TT:0.3)



Overall Design of Phase I (option 2)

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



Phase II

Primary Questions

- Does oral tirzepatide provide substantial benefit over placebo in reducing HbA1c and helping with weight loss in overweight T2DM patients?
- Which doses best balance efficacy and safety?

Primary Endpoints

- mean change in HbA1c (%)
- mean change in body weight (kg)

Secondary Endpoints

- % of patients achieving HbA1c < 7%
- mean change in fasting plasma glucose
- avg % change in body weight (kg)

Duration: 26 weeks

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

Design Options

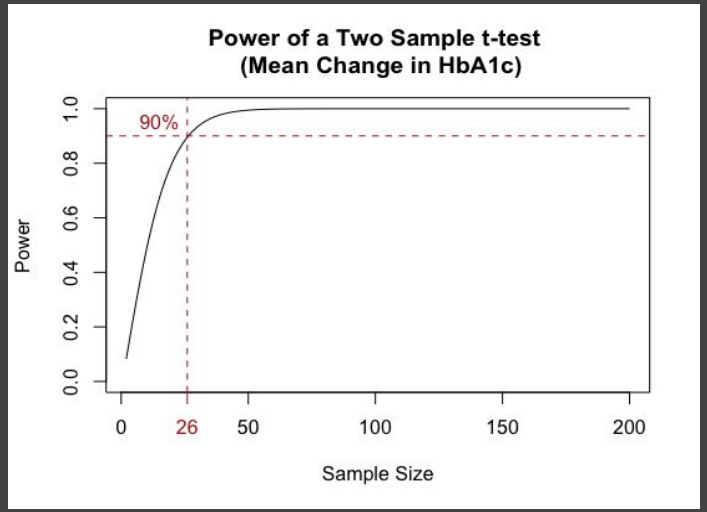
1. First POC, then DF
2. Simultaneous POC + DF
3. Seamless Ph2+3

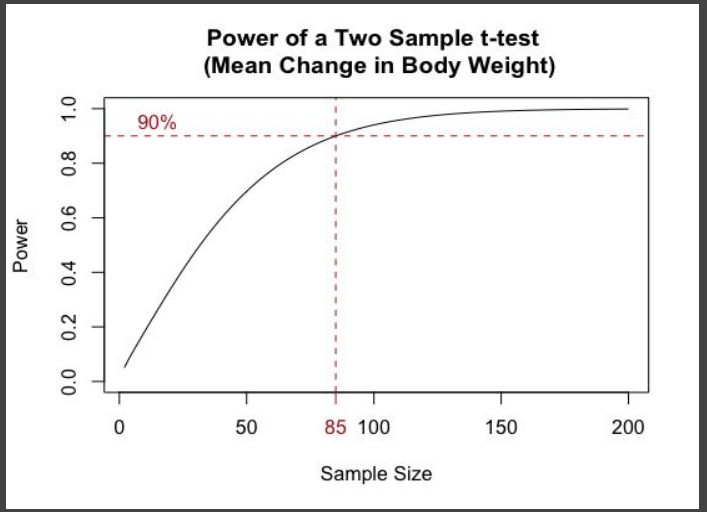
Sample Size Determination

Procedure: 2 sample t-test
Power: 90%
Type I error: 5% (two-sided)

power.t.test() function in R

Discontinuation or rescue medicine: 15% of patients



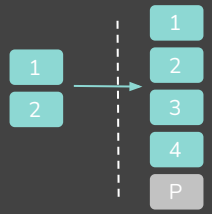


Change in HbA1c
Effect size: 1%
Standard deviation: 1.1%
Without adjustment: 26/arm
With adjustment: 32/arm

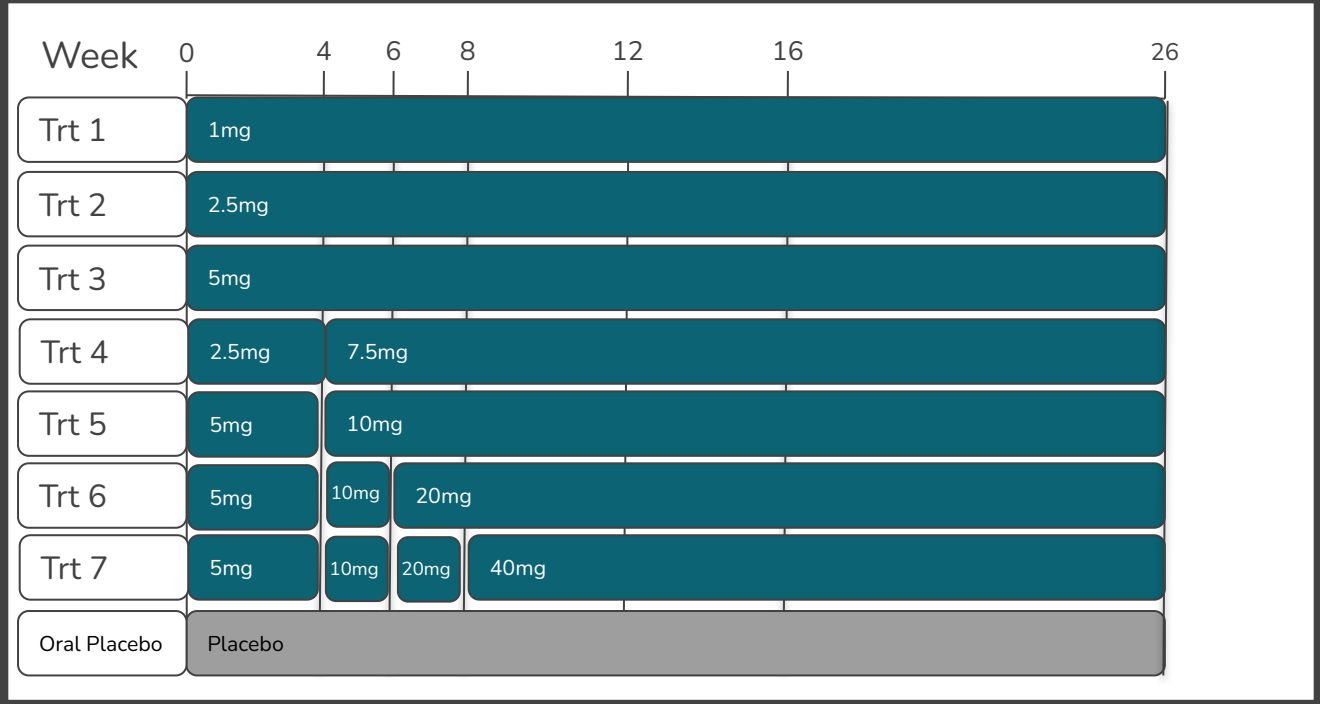
Change in Body Weight
Effect size: 2kg
Standard deviation: 4kg
Without adjustment: 85/arm
With adjustment: 100/arm

Required sample size: 100/arm

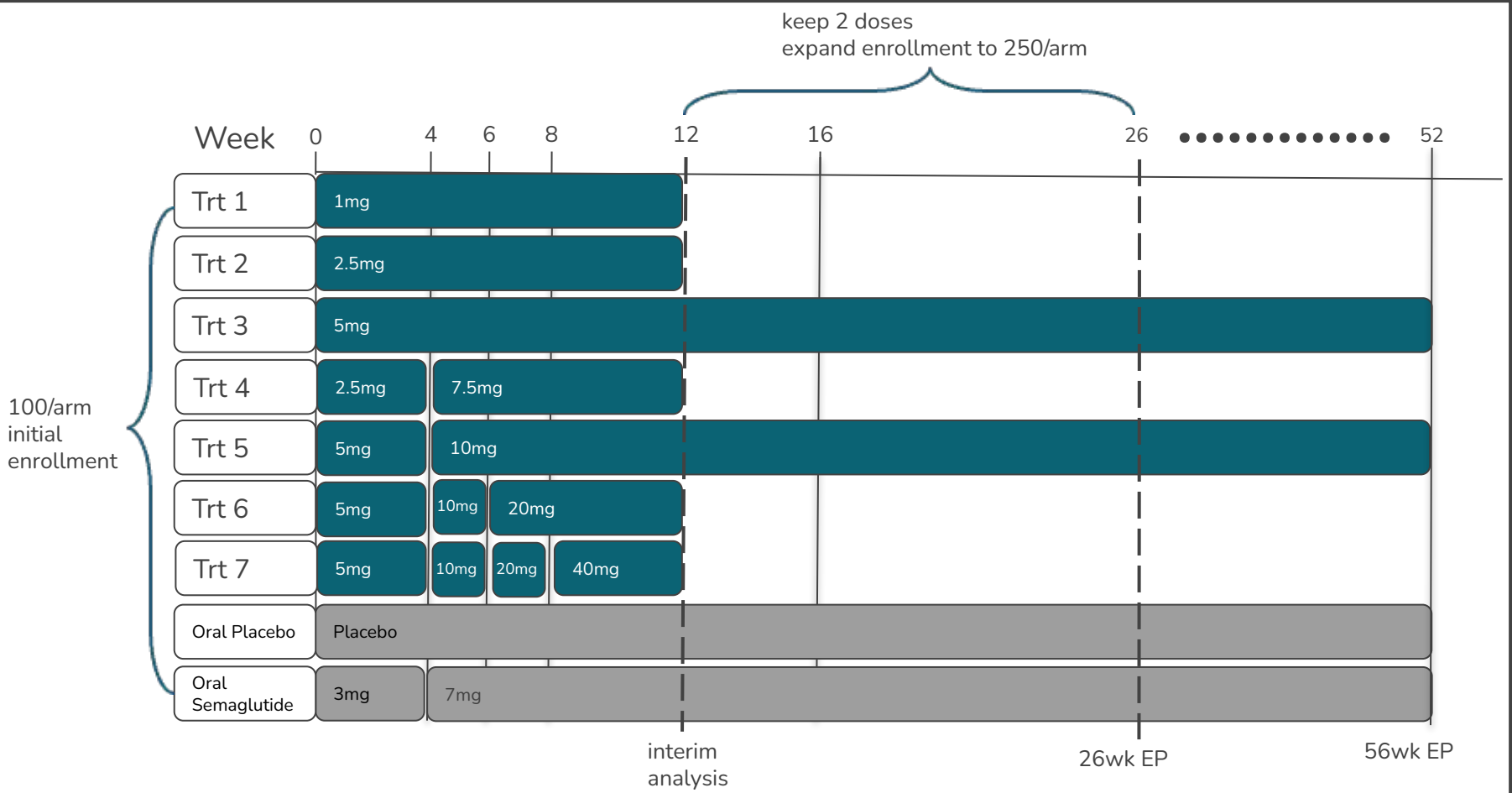
Phase II Design Options

	Option 1	Option 2	Option 3
Basic Design	POC (2 ET) then DF 2 ET  4 ET 1 placebo	Simultaneous POC + DF 7 ET 1 placebo 	Seamless Ph2-3 7 ET keep 2 after 26wk EP 1 placebo 1 AC 
Sample size	100/arm	100/arm	100/arm initially, expand to 250/arm 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 + placebo + AC until 52wk EP

Option 2: Simultaneous POC + DF



Option 3: Seamless Ph2/3



Phase III

Primary question:
- Investigate the efficacy, safety, and tolerability of oral trizepitide added to metformin.

Primary endpoint:
- Mean change in HbA1c
- Mean change in body weight (kg)

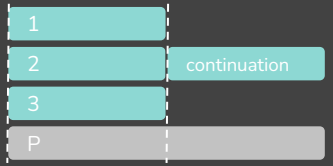
Secondary Endpoints:
- Change in 2 hour plasma glucose,
- Change is body weight, and
- Change in fasting plasma glucose.

Duration: 26 weeks (52 week follow up)

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

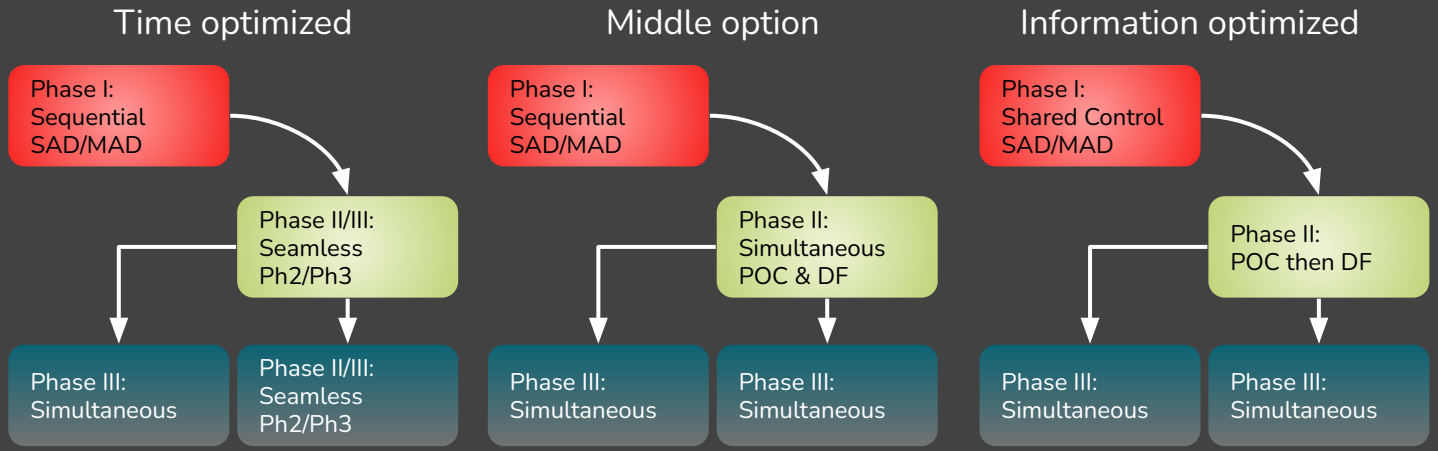
Additional FDA guidance:
- Replicable studies
- Safety database should include:
  - at least 4,000 patient-years of exposure in Ph3,
  - at least 1,500 exposed for at least 1 year, and
  - at least 500 exposed for at least 2 years.
- Comorbid conditions or related conditions:
  - at least 500with stage 3/4 chronic kidney disease,
  - at least 600 with established CV disease, and
  - at least 600 older than 65 years.

Phase III Design Options

	Option 1	Option 2
Basic Design	Simultaneous treatment + placebo 3 ET 52 wk + aditional 52 wk 1 placebo 	Seamless Ph2-3 7 ET keep 2 after 26wk EP 1 placebo 1 AC 
Sample size	600/arm of active treatment continuation group of 600 patients	100/arm initially, expand to 250/arm after 26wk EP
Pros/Cons	Would obtain the 1,500 patient exposure of 1 year and the 500 patient exposure of 2 year requirement. Long time for patients to stay in study	smaller sample size for Ph2/Ph3 Potentially faster Logistically difficult
Other	Take 3 doses into phase 3 for sample size purposes. Could switch to 2 doses at around 800/arm.	Continue 2 doses + placebo + AC until 52wk EP

- Still need to show replicability, potentially combine both options or do two of option 1, possibly offset.

Full experiment options



Pros & Cons:	Shortest overall time Risky/aggressive Need large sample size for Phase III	Move quickly through phase I and II Gain plenty of information in phase III	Gain as much information possible, Will for sure meet FDA safety database. Slower than the other options