Type 2 Diabetes Clinical Trial Plan: Oral Tirzepatide

Nathen Byford, Taylor Grimm, Emmanuel Sarfo Fosu, and Bel Zhang

Overview

- Type 2 diabetes (T2DM), a metabolic disorder associated with impaired glucose homeostasis where HbA1c is 6.5% or higher (NDA 215866).
- The main competitors for the proposed treatment are Semaglutide (Oral), Semaglutide (Injectable) and Tirzepatide (Injectable).

- Our Proposed treatment is an Oral Tirzepatide
  - Improve blood glucose control in adults with T2DM
  - Provide substantial weight loss benefits

Primary questions

- **Phase I**
  - To investigate the safety and tolerability of single and multiple doses of oral tirzepatide to healthy subjects and patients with T2DM.

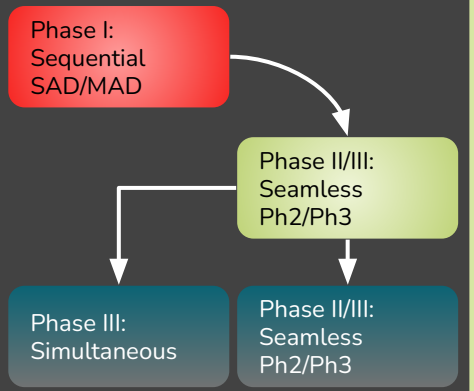
- **Phase II**
  - Does oral tirzepatide provide substantial benefit over placebo in reducing HbA1c and helping with weight loss in overweight T2DM patients?
  - Which doses best balance efficacy and safety?

- **Phase III**
  - Investigate the efficacy, safety, and tolerability of oral tirzepatide added to metformin.

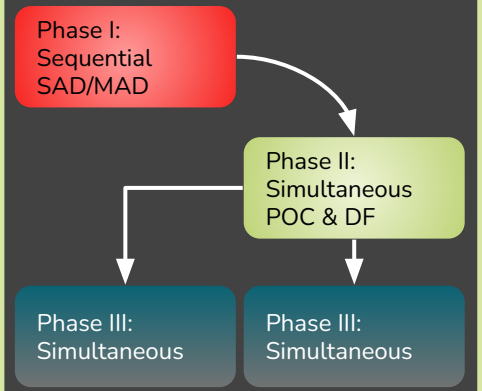
Full experiment options

Recommended Option

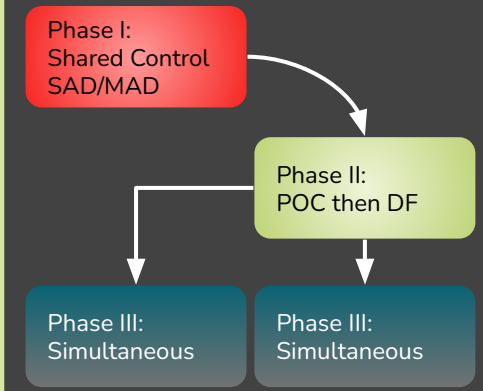
Time optimized



Middle option



Information optimized



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

Disruption

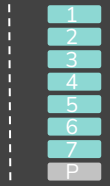
“Preclinical reproductive toxicology data was delayed (24 weeks). You will not be able to enroll females in your phase 2 studies until the reproductive toxicology data is available.”

Implications of disruption on design

- Cannot immediately begin our recommended Phase 2 (simultaneous POC+DF)
- May need to delay Phase 2 by about 6 months.
- Significant setback and increased costs.
- Possible to still enroll older (postmenopausal) females because reproductive effects are not an issue.
    - Average age of patients in competitor Phase 2 T2DM trials is around 56

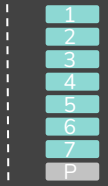
Drug	Average Age (sd)	% Female
SC Tirzepatide	57.2 (8.54)	46.8%
SC Semaglutide	55.0 (9.8)	35.0%
Oral Semaglutide	57.1 (10.6)	37.3%

Disruption: Phase 2 Design Options

	Option 1	Option 2	Option 3
Design	Simultaneous POC + DF Wait 6 months 7 ET 1 placebo 	Simultaneous POC + DF No delay 7 ET 1 placebo 	12 wk POC, then 24 wk DF POC High Med Low Wait for tox. data DF 
Design Notes	Start original design plan after delay	Men + older/postmenopausal women	Men + older/postmenopausal women in POC Entire patient pop. in DF
Pros	No additional planning required Uses entire target population	Fastest (no delay)	Gain information during delay Uses entire target population
Cons	Slow (full 6 month delay) No information gain during delay	Proceed to Ph3 at sponsor risk	Ph2 still delayed by 6 months Potentially more expensive

Disruption: Phase 2 Design Options

Recommended Option

	Option 1	Option 2	Option 3
Design	Simultaneous POC + DF Wait 6 months 7 ET 1 placebo 	Simultaneous POC + DF No delay 7 ET 1 placebo 	12 wk POC, then 24 wk DF 
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Extra slides

Diabetes in the United States

- By ADA, in 2021, 38.4 million Americans, or 11.6% of the population, had diabetes.
- 2 million Americans have type 1 diabetes, including about 304,000 children and adolescents
- The percentage of Americans age 65 and older remains high, at 29.2%, or 16.5 million seniors (diagnosed and undiagnosed).

Appendix Table 5. Age-adjusted prevalence of prediabetes according to various definitions of hyperglycemia[a] among adults aged 18 years or older, United States, 2017–2020.

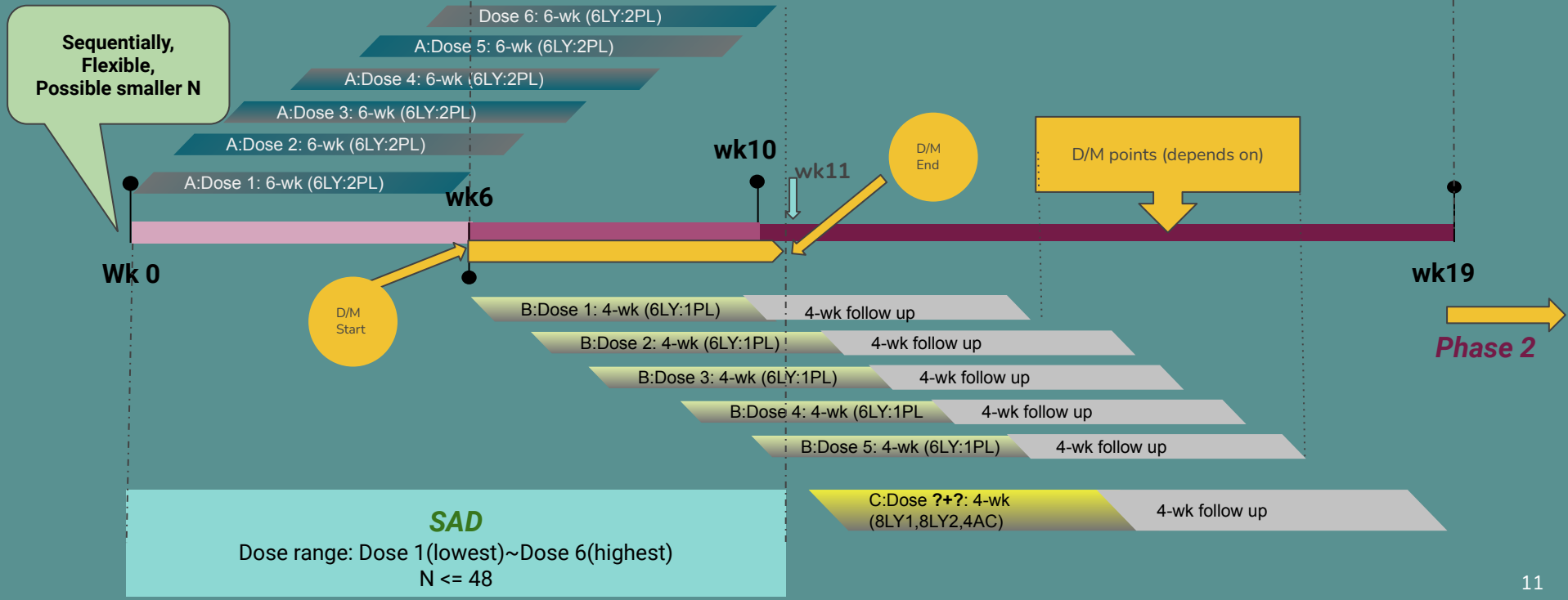
Characteristic	Definition 1 Percentage (95% CI)	Definition 2 Percentage (95% CI)	Definition 3 Percentage (95% CI)
Total	36.5 (34.2–38.8)	22.2 (20.5–24.0)	10.8 (9.7–11.9)
Age, years[a]			
18–44	27.8 (24.0–32.0)	12.6 (10.7–14.8)	5.8 (4.6–7.4)
45–64	44.8 (41.7–47.9)	30.2 (26.5–34.3)	13.8 (12.0–15.9)
≥65	48.8 (44.3–53.2)	38.1 (34.5–41.8)	20.8 (17.4–24.6)
Sex			
Men	41.0 (37.3–44.8)	22.7 (20.4–25.3)	11.4 (9.6–13.4)
Women	32.0 (28.9–35.2)	21.6 (18.6–25.0)	10.2 (8.3–12.4)

Overall Design of Phase I

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

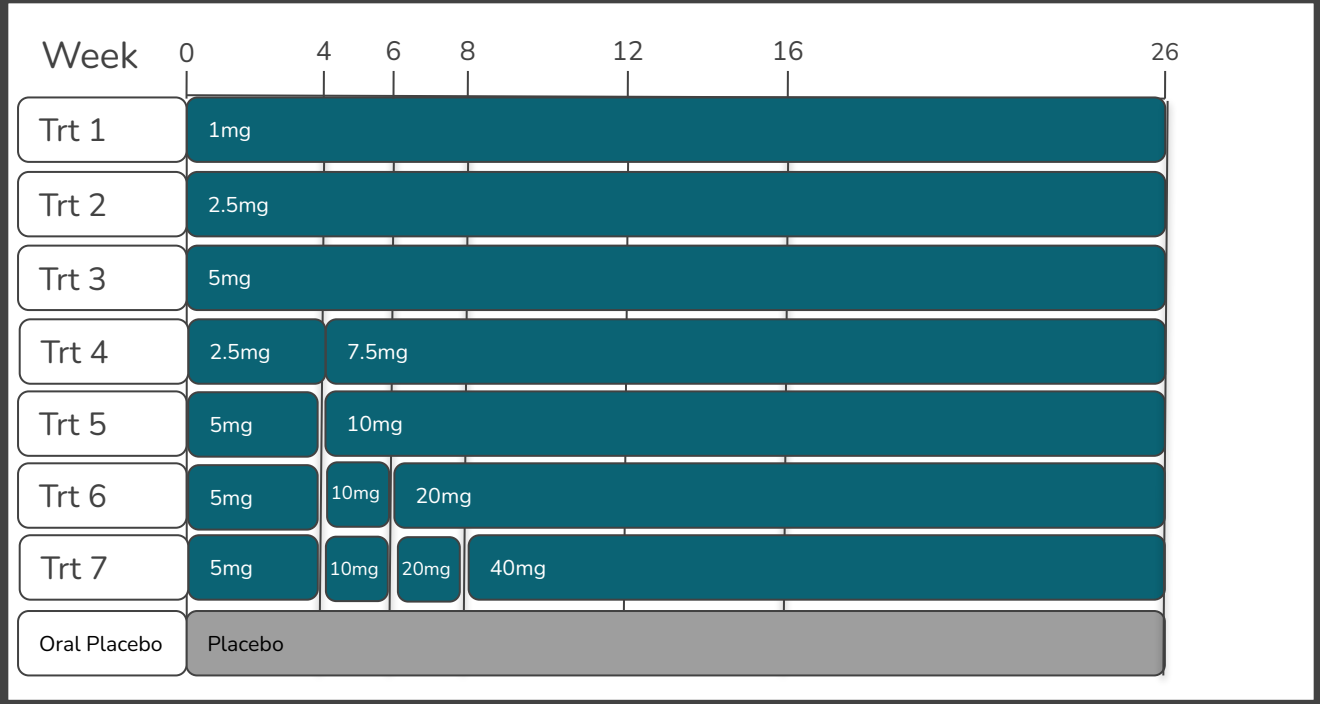
$Pr(p_i|data)$: 25 ~50 ~70 Rule
Es: $Pr_e < 0.25$
DeEs: $Pr_d > 0.50$

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

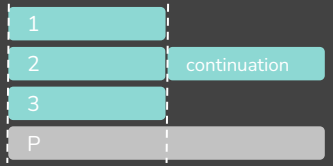
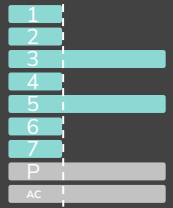


SAD
Dose range: Dose 1(lowest)~Dose 6(highest)
N <= 48

Option 2: Simultaneous POC + DF



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.