# 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
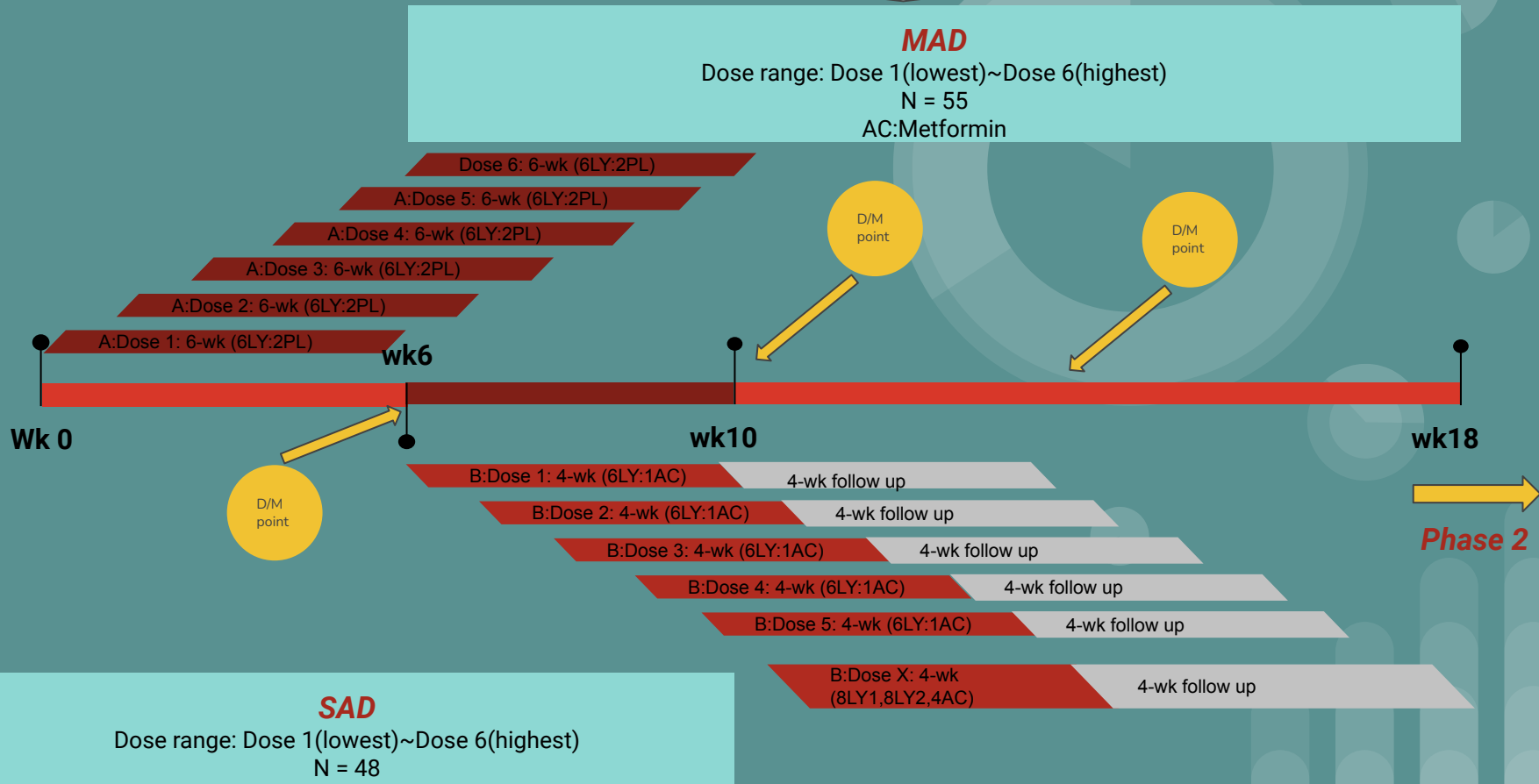- BMI 20.0–29.9 kg/m²

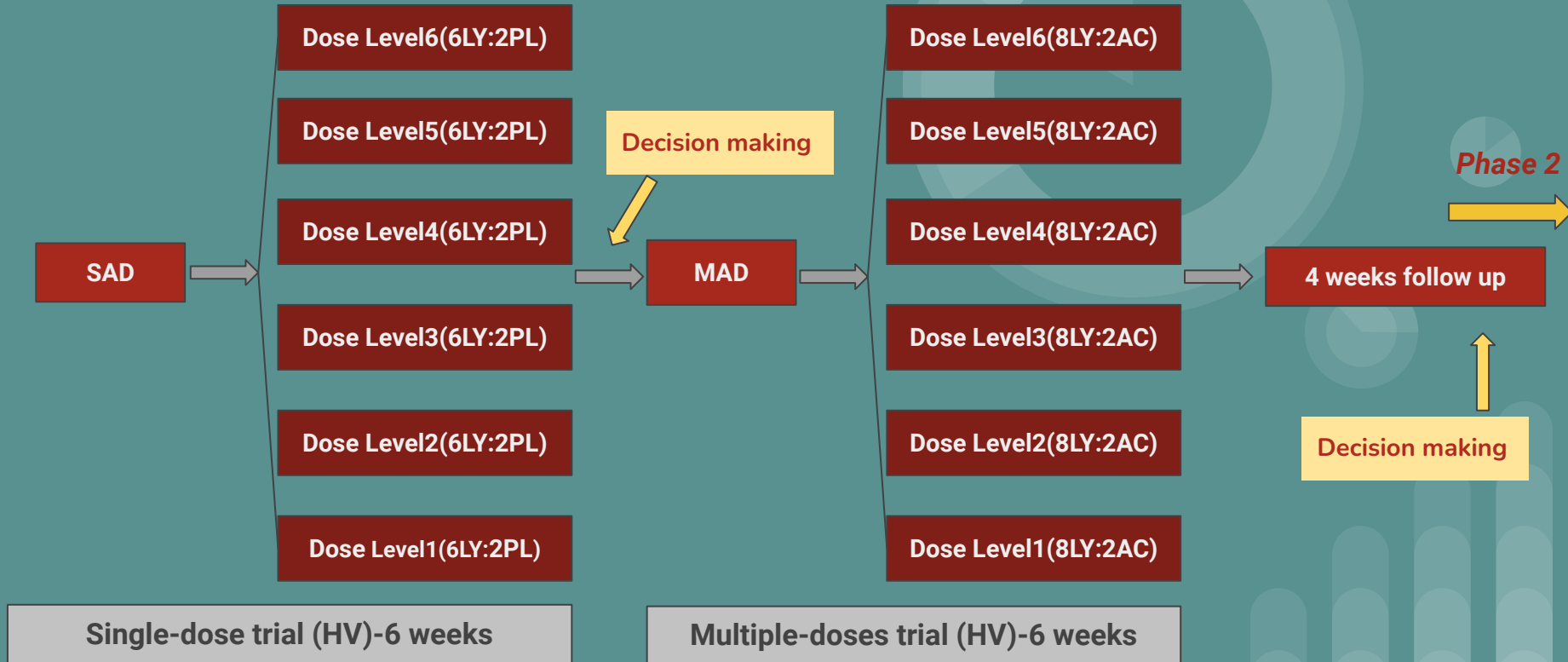## Part C: T2DM

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

Dose 6: 6-wk (6LY:2PL)
A:Dose 5: 6-wk (6LY:2PL)
A:Dose 4: 6-wk (6LY:2PL)
A:Dose 3: 6-wk (6LY:2PL)
A:Dose 2: 6-wk (6LY:2PL)
A:Dose 1: 6-wk (6LY:2PL)

**wk6**

D/M point

D/M point

**Wk 0**

**wk10**

**wk18**

D/M point

B:Dose 1: 4-wk (6LY:1AC)    4-wk follow up
B:Dose 2: 4-wk (6LY:1AC)    4-wk follow up
B:Dose 3: 4-wk (6LY:1AC)    4-wk follow up
B:Dose 4: 4-wk (6LY:1AC)    4-wk follow up
B:Dose 5: 4-wk (6LY:1AC)    4-wk follow up
B:Dose X: 4-wk (8LY1,8LY2,4AC)    4-wk follow up

*Phase 2*

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

# Overall Design of Phase I (option 2)



Dose Level6(6LY:2PL)

Dose Level5(6LY:2PL)

Dose Level4(6LY:2PL)

Dose Level3(6LY:2PL)

Dose Level2(6LY:2PL)

Dose Level1(6LY:2PL)

SAD

Decision making

MAD

Dose Level6(8LY:2AC)

Dose Level5(8LY:2AC)

Dose Level4(8LY:2AC)

Dose Level3(8LY:2AC)

Dose Level2(8LY:2AC)

Dose Level1(8LY:2AC)

4 weeks follow up

*Phase 2*

Decision making

**Single-dose trial (HV)-6 weeks**

**Multiple-doses trial (HV)-6 weeks**

# 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

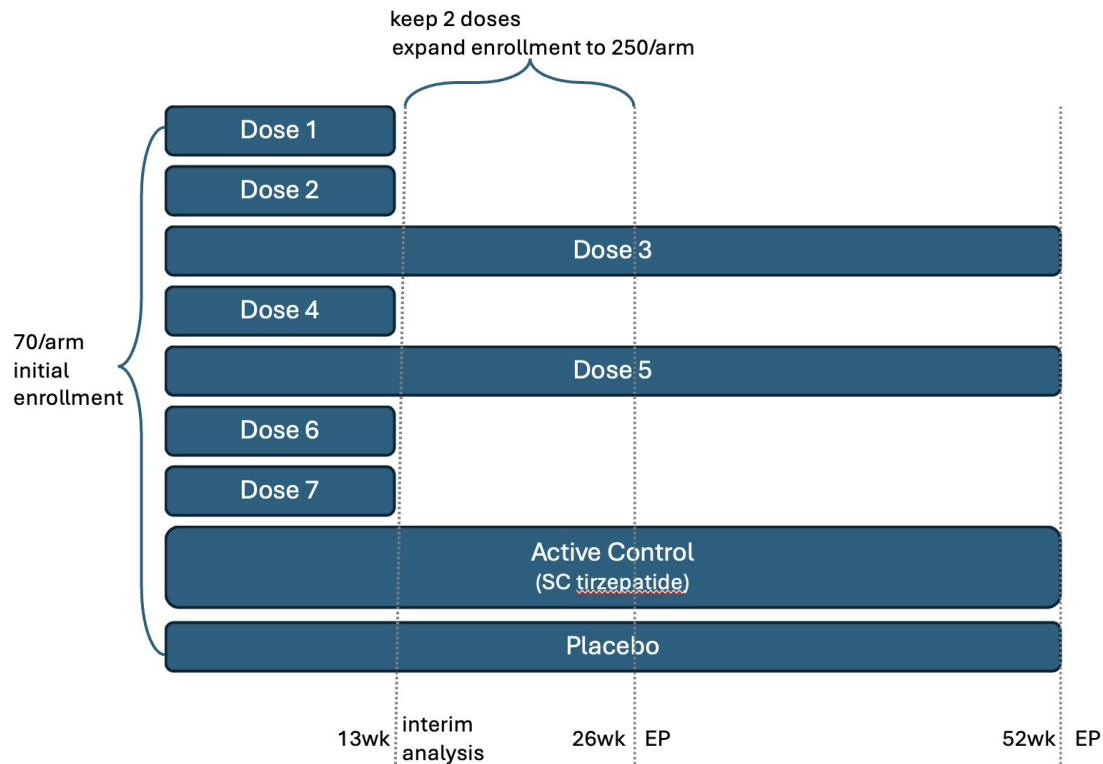| | Option 1 | Option 2 | Option 3 |
|---|---|---|---|
| Basic Design | POC then DF<br><br>POC: 2 doses<br>DF: 4 oral doses<br>1 placebo | Simultaneous POC + DF<br><br>7 oral doses<br>1 SC tirzepatide<br>1 placebo | Seamless Ph2-3<br><br>7 initial doses, keep 2 after 26wk EP<br>1 SC tirzepatide<br>1 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<br><br>slower than other options | quicker to Ph3 higher upfront cost/risk than Option 1 | smaller sample size for Ph2/Ph3 potentially faster<br><br>logistically difficult |
| Other | | | continue 2 doses + AC + placebo until 52wk EP |

# Example: Simultaneous POC+DF (Option 2)

(Novo Nordisk semaglutide tablet Phase 2 design)



| Week | | 0 2 4 6 8 12 16 20 24 26 31 |
|---|---|---|
| **Dose range** Oral OD | 1 | 2.5 mg — Follow-up |
| Oral OD | 2 | 2.5 mg / 5.0 mg — Follow-up |
| Oral OD | 3 | 5.0 mg / 10 mg — Follow-up |
| Oral OD | 4 | 5.0 mg / 10 mg / 20 mg — Follow-up |
| Oral OD | 5 | 5.0 mg / 10 mg / 20 mg / 40 mg — Follow-up |
| **Escalation** Oral OD | 6 | 5.0 mg / 10 mg / 20 mg / 40 — Follow-up |
| Oral OD | 7 | 5.0 / 10 / 20 / 40 mg — Follow-up |
| **Comparators** Oral OD | 8 | Placebo — Follow-up |
| s.c. OW | 9 | 0.25 mg / 0.50 mg / 1.0 mg s.c. semaglutide, open-label — Follow-up |

OD: once-daily, OW: once-weekly

# Seamless Ph2/3 (Option 3)



**Seamless Ph2/3 Design Option**

keep 2 doses
expand enrollment to 250/arm

Dose 1

Dose 2

Dose 3

Dose 4

Dose 5

Dose 6

Dose 7

Active Control
(SC tirzepatide)

Placebo

70/arm
initial
enrollment
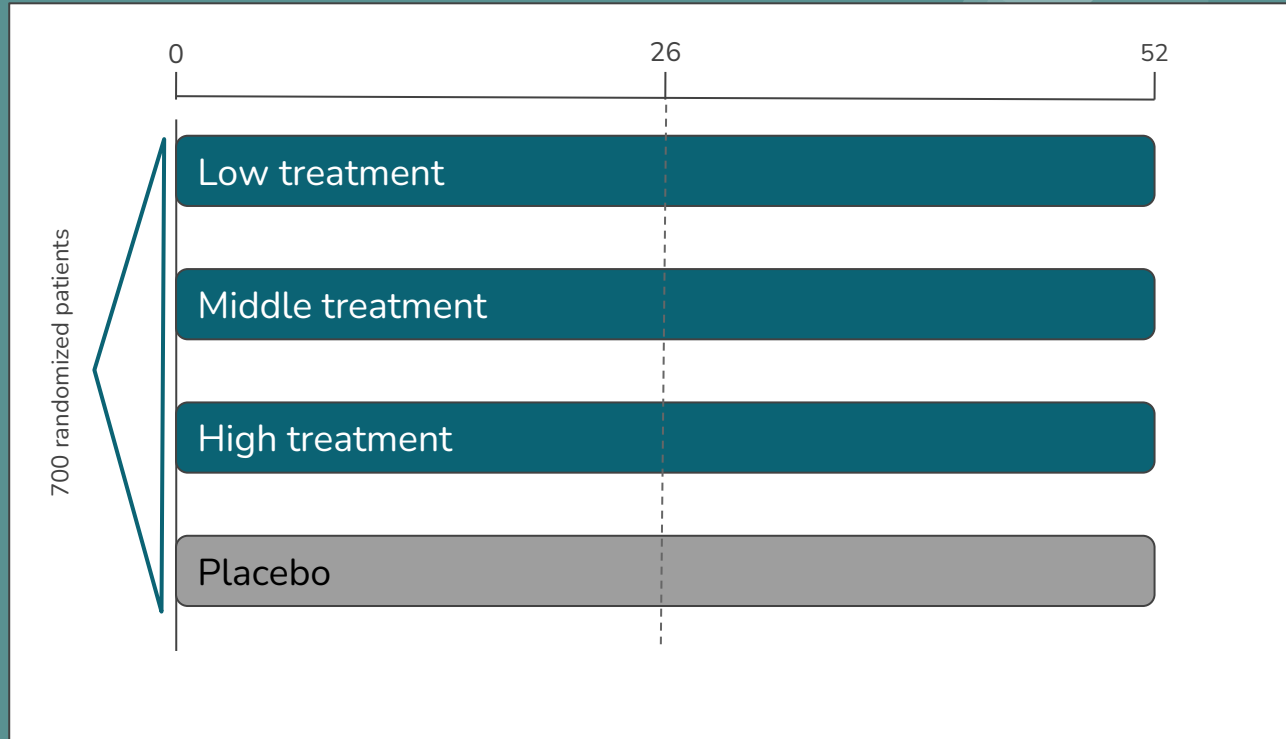
13wk — interim analysis — 26wk — EP — 52wk — EP

# 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 interim analysis | Seamless Ph2/3 |
| Sample size | 700 randomized to about 175 per arm | 700 | 500 - 600 |
| Cosiderations | Choice of treatment dosages | Interim analysis at 13 weeks  Cost | FDA may require larger safety database |

# Trial Plan Overview