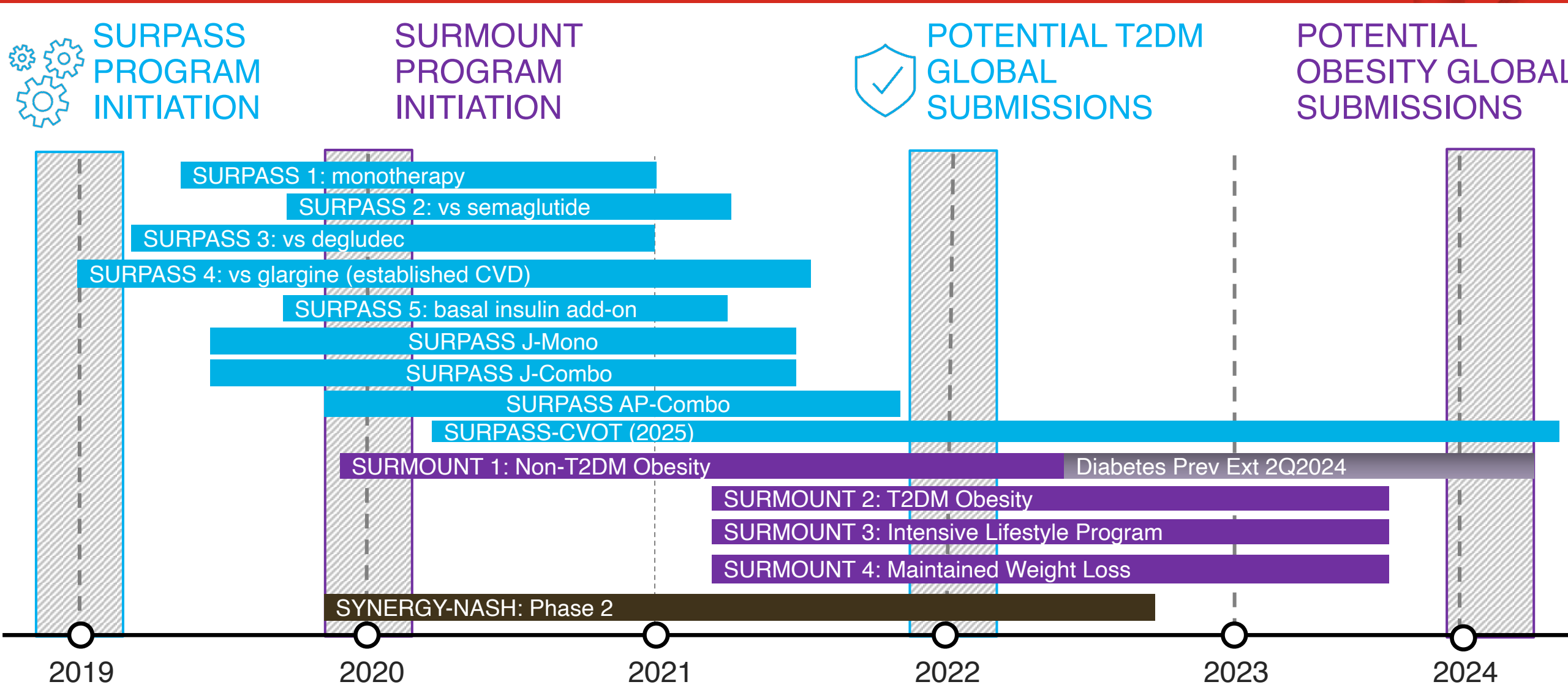
Disclosure/Disclaimer

- The information contained in this slide kit is intended and should be used for scientific and/or educational purposes and will not be used for promotional purposes.

- Tirzepatide is an investigational drug and has not been approved for marketing in Canada.

Tirzepatide Clinical Trial Program Overview

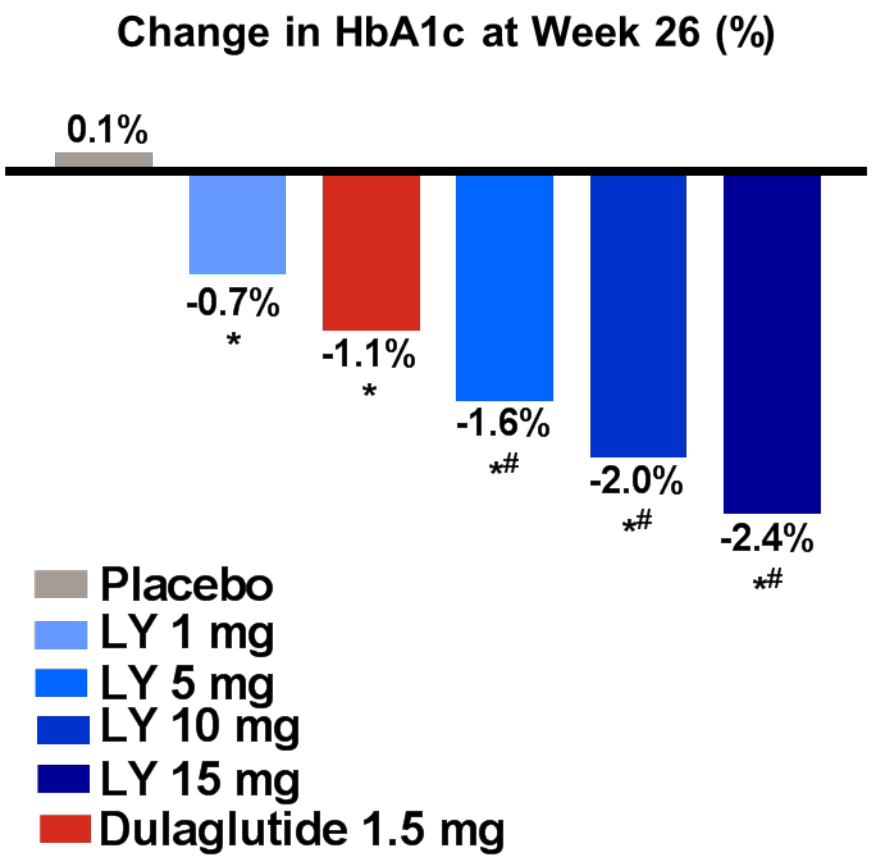
Diabetes, Obesity and NASH Clinical Trial Program

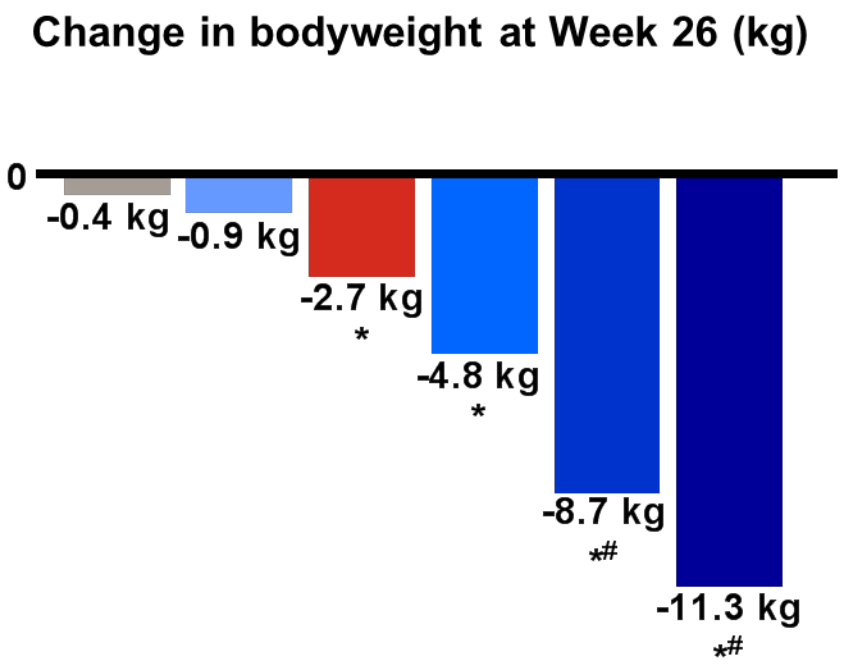


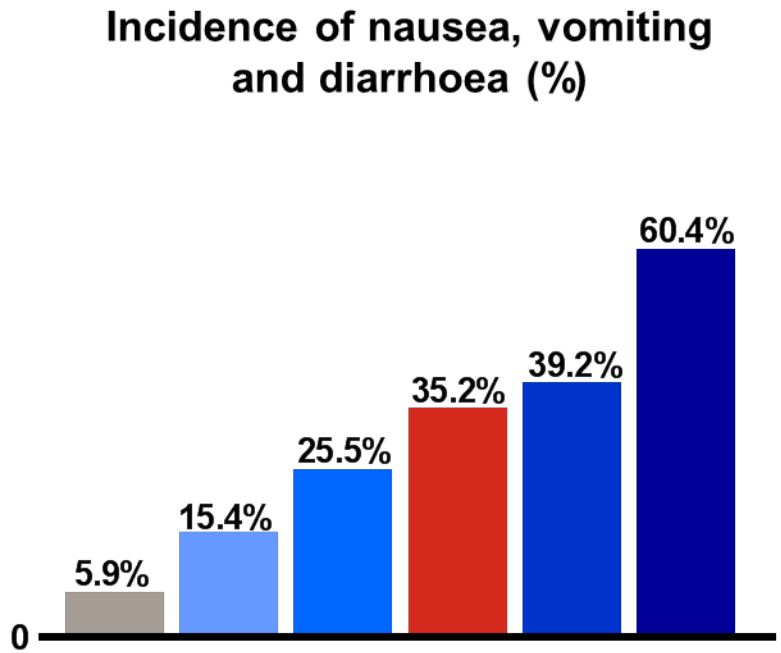
https://investor.lilly.com/webcasts-and-presentations

Phase 2 findings in patients with diabetes

Summary: HbA1c, Weight Loss, and GI Side Effects at Week 26 - Phase 2B Findings





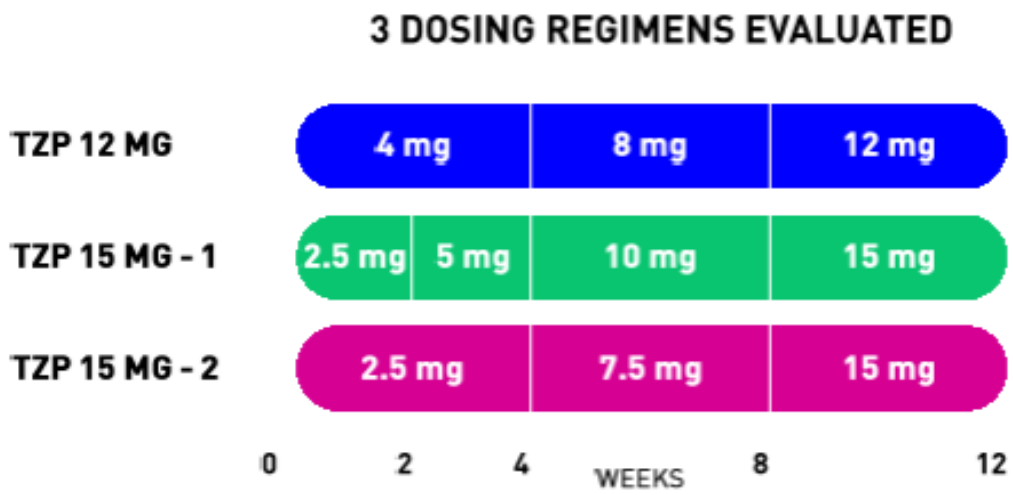


Data for change in HbA1c and bodyweight presented are LS mean ± SE, MMRM on treatment analysis. *,#p<.05 vs placebo and vs. dulaglutide 1.5 mg, respectively.
Frias JP et al. *Lancet* 2018; (in press) DOI: 10.1016/S0140-6736(18)32260-8

HbA1C: glycosylated hemoglobin
MMRM: mixed effect model repeat
LS: least square
SE: standard error

Phase 2 Dosing - Study Design

PHASE 2 DOSING STUDY

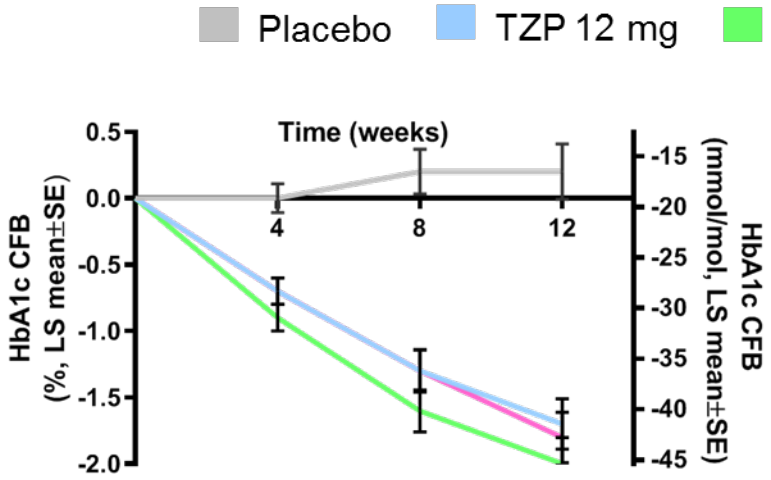


- Different tirzepatide starting doses and different dose escalation increments assessed
- 3-month, randomized, double-blind, placebo-controlled study with 111 total patients

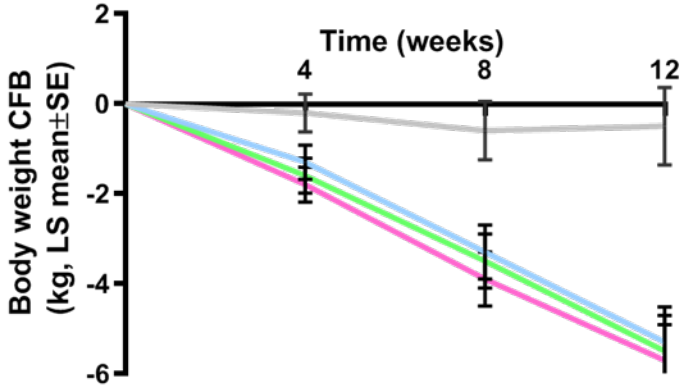
Frias et al. Diabetes Obesity Metabolism 2020 DOI: 10.1111/dom.13979

Phase 2 Dosing Study: EFFICACY OVER TIME AND TREATMENT DISCONTINUATIONS[1,2]

Change in HbA1c through 12 Weeks



Change in Body Weight through 12 Weeks



Discontinuations	Placebo (N=26) n (%)	TZP 12 mg (N=29) n (%)	TZP 15 mg-1 (N=28) n (%)	TZP15 mg-2 (N=28) n (%)
Overall treatment discontinuations	6 (23.1%)	2 (6.9%)	6 (21.4%)	2 (7.1%)
Treatment discontinuation due to AEs	1 (3.8%)	1 (3.4%)	1 (3.6%)	0

AE=adverse events; CFB=change from baseline; HbA1c=glycated hemoglobin; LS=least squares; SE=standard error

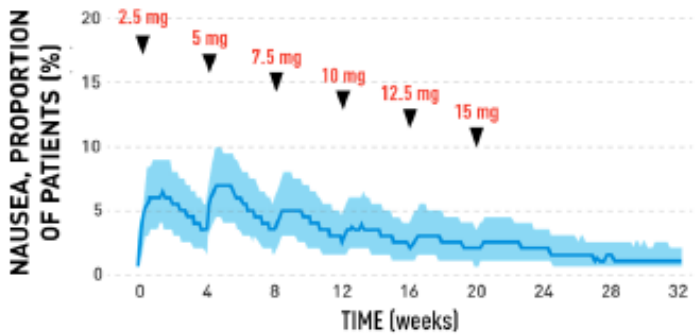
1. Frias J, Nauck M A, Van J, et al. 993-P: A 12-Week, Randomized, Placebo-Controlled Study Assessing the Efficacy and Safety of Three Dose-Escalation Algorithms of Tirzepatide, a Novel Dual GIP and GLP-1 Receptor Agonist, in Patients with Type 2 Diabetes. In: Proceedings from the 79 th Scientific Sessions of the American Diabetes Association; June 7-11, 2019; Can Francisco, CA.
2. Data on file, Eli Lilly and Company and/or one of its subsidiaries.

Tirzepatide Phase 3 Dosing

CONCLUSIONS FROM DOSING STUDY

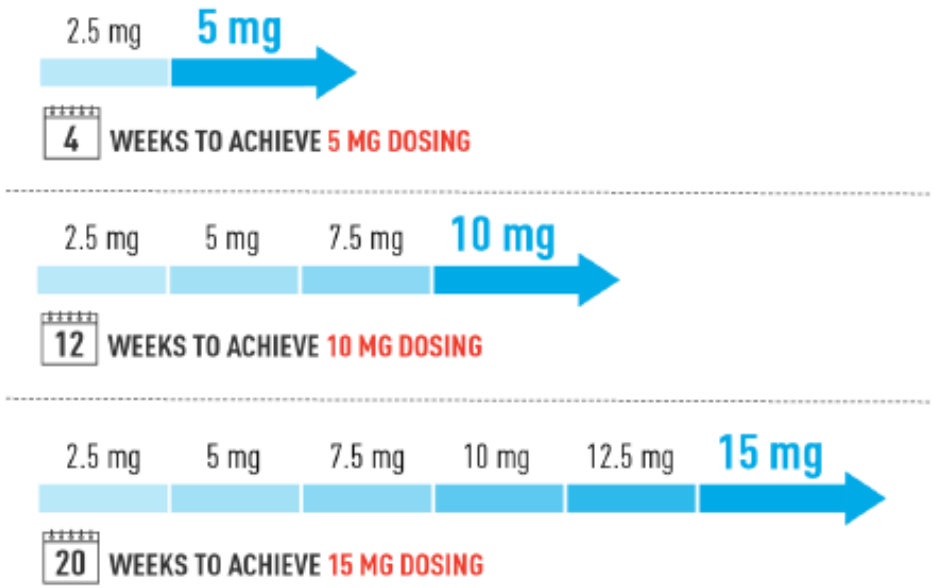
- **Consistent efficacy:** HbA1c reduction and weight loss
- Dose escalation resulted in an **improved tolerability profile**
- Treatment **discontinuation rates were lower** vs. previously disclosed Phase 2b study
- **No discontinuation imbalance due to adverse events** vs. placebo

STUDY RESULTS AND EXPOSURE MODELING INFORMED PHASE 3 DOSING



PHASE 3 DOSE SCHEDULE

Step through doses (2.5mg increments) expected to improve tolerability profile while achieving breakthrough efficacy goals



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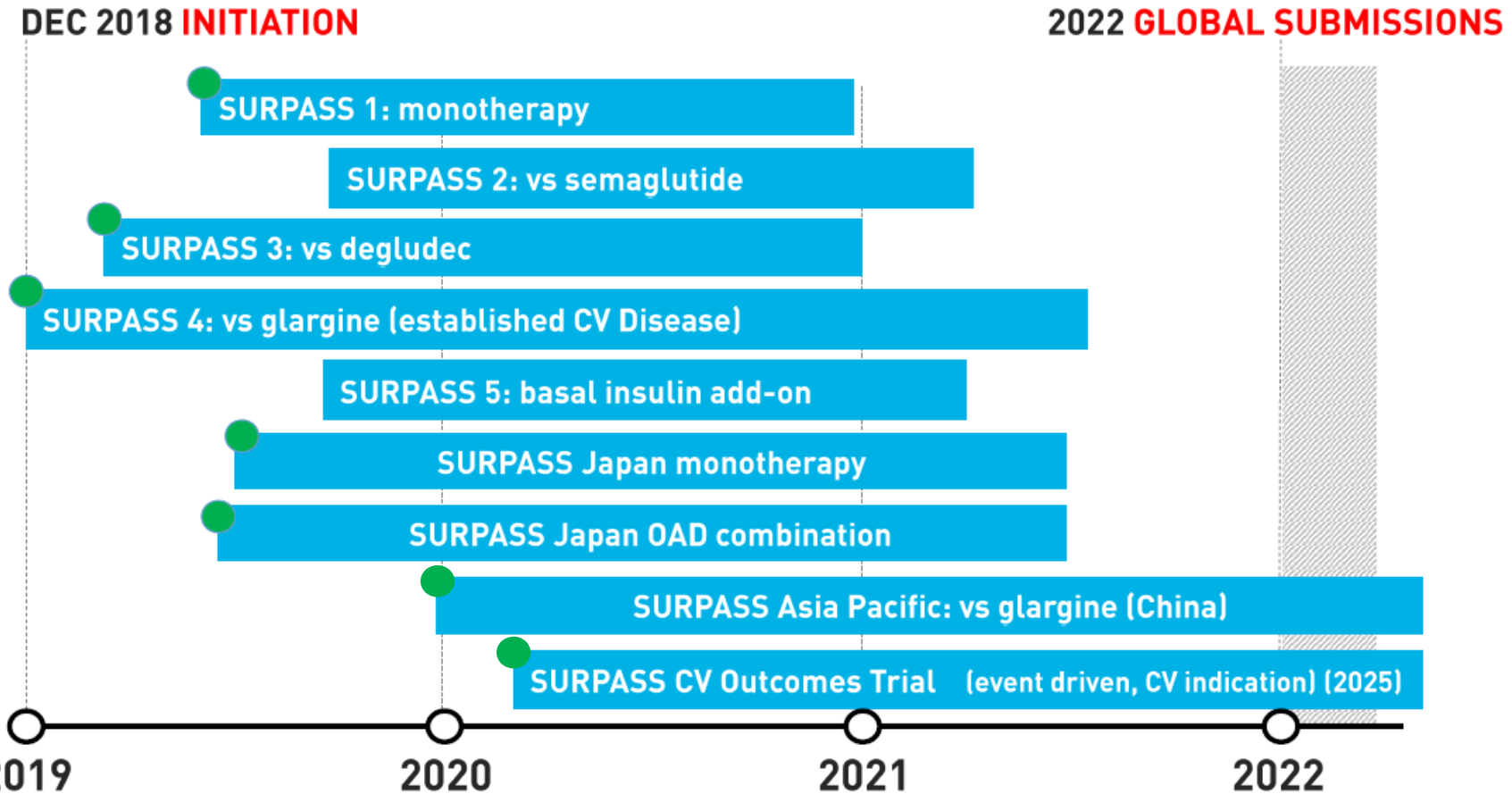
Tirzepatide Phase 3 Clinical Trial Program

SURPASS TYPE 2 DIABETES PROGRAM

Five type 2 diabetes Phase 3 studies initiated



OTHER INDICATIONS

2019

Obesity **Phase 3** – start of SURMOUNT program

NASH **Phase 2** – start of SYNERGY-NASH program

https://investor.lilly.com/webcasts-and-presentations

SURPASS-1 - A Study of Tirzepatide (LY3298176) in Participants With Type 2 Diabetes Not Controlled With Diet and Exercise Alone (SURPASS-1)

- **Primary Efficacy Objective**
  - Change from Baseline in HbA1c (Baseline to Week 40)

- **Key Secondary Efficacy Objectives:**
  - Mean change in body weight
  - Proportion of patients with HbA1c target values of <7.0% (<53 mmol/mol)
  - Mean change in fasting serum glucose (FSG) (central laboratory)
  - Proportion of patients with HbA1c target values of <5.7% (<39 mmol/mol)

A Study of Tirzepatide (LY3298176) in Participants With Type 2 Diabetes Not Controlled With Diet and Exercise Alone - Full Text View - ClinicalTrials.gov

Key Inclusion Criteria

- Have been diagnosed with type 2 diabetes mellitus (T2DM).
- Are naïve to diabetes injectable therapies and have not used any oral antihyperglycemic medications (OAMs) during the 3 months preceding screening.
- Have HbA1c between ≥7.0% and ≤9.5%.
- Be of stable weight (± 5%) for at least 3 months before screening.
- Have a BMI ≥23 kilograms per meter squared (kg/m²) at screening.

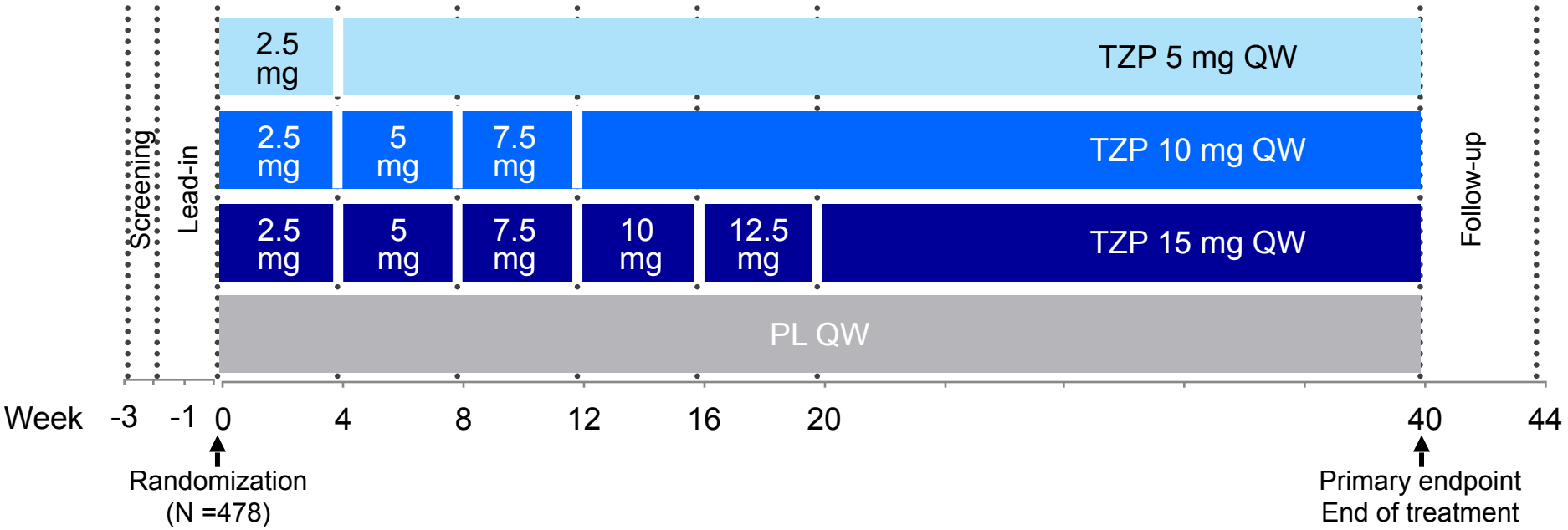
A Study of Tirzepatide (LY3298176) in Participants With Type 2 Diabetes Not Controlled With Diet and Exercise Alone - Full Text View - ClinicalTrials.gov

Key Exclusion Criteria

- Have type 1 diabetes mellitus.
- Have had chronic or acute pancreatitis any time prior to study entry.
- Have proliferative diabetic retinopathy or diabetic maculopathy or nonproliferative diabetic retinopathy requiring acute treatment.
- Have disorders associated with slowed emptying of the stomach, or have had any stomach surgeries for the purpose of weight loss.
- Have an estimated glomerular filtration rate <30 mL/minute/1.73 m^2.
- Have had a heart attack, stroke, or hospitalization for congestive heart failure in the past 2 months.
- Have a personal or family history of medullary thyroid carcinoma or personal history of multiple endocrine neoplasia syndrome type 2.
- Have been taking weight loss drugs, including over-the-counter medications during the last 3 months.

A Study of Tirzepatide (LY3298176) in Participants With Type 2 Diabetes Not Controlled With Diet and Exercise Alone - Full Text View - ClinicalTrials.gov

Study Design and baseline



Key baseline characteristics:

- Treatment naïve: 54.2%
- Mean duration of diabetes: 4.7 years
- Baseline HbA1c: 7.9%
- Baseline Body Weight: 85.9kg

All participants in the tirzepatide treatment arms started the study at a dose of tirzepatide 2.5 mg once-weekly and then increased the dose in a step-wise approach at four-week intervals to their final randomized maintenance dose of 5 mg (via a 2.5 mg step), 10 mg (via steps at 2.5 mg, 5 mg and 7.5 mg) or 15 mg (via steps at 2.5 mg, 5 mg, 7.5 mg, 10 mg and 12.5 mg).

SURPASS 1 Press Release December 9 2020 Lilly's tirzepatide significantly reduced A1C and body weight in people with type 2 diabetes | Eli Lilly and Company

SURPASS 1 Top Line Results – Efficacy Estimand*

	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg	Placebo
A1c reduction (%) Baseline- 7.9	-1.87	-1.89	-2.07	+0.04
Placebo-adjusted A1C reduction	-1.91%	-1.93%	-2.11%	N/A
Weight reduction kg (%) Baseline 85.9 kg	-7.0 (-7.9%)	-7.8 (-9.3%)	-9.5 (-11.0%)	-0.7 (-0.9%)
Placebo-adjusted weight reduction kg	-6.3	-7.1	-8.8	N/A
Percent of participants achieving A1C <7%	86.8	91.5	87.9	19.6
Percent of participants achieving A1C <5.7%	33.9	30.5	51.7	0.9

*Efficacy estimand represents efficacy prior to discontinuation of study drug or initiating rescue therapy for persistent severe hyperglycemia.
All three tirzepatide doses led to statistically significant A1C and body weight reductions from baseline and also reached statistical significance in the percentage of participants who achieved an A1C of less than 7 percent or less than 5.7 percent.
SURPASS 1 Press Release December 9 2020 Lilly's tirzepatide significantly reduced A1C and body weight in people with type 2 diabetes | Eli Lilly and Company

SURPASS 1 Top Line Results – Treatment Regimen Estimand*

	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg	Placebo
A1c reduction (%) Baseline- 7.9	-1.75	-1.71	-1.69	-0.09
Weight reduction (kg) Baseline- 85.9 kg	-6.3kg	-7.0kg	-7.8kg	-1.0kg
Percent of participants achieving A1C <7%	81.8	84.5	78.3	23.0
Percent of participants achieving A1C <5.7%	30.9	26.8	38.4	1.4

*Treatment-regimen estimand represents the efficacy irrespective of adherence to the investigational medicine or introduction of rescue therapy for persistent severe hyperglycemia.
SURPASS 1 Press Release December 9 2020 Lilly's tirzepatide significantly reduced A1C and body weight in people with type 2 diabetes | Eli Lilly and Company

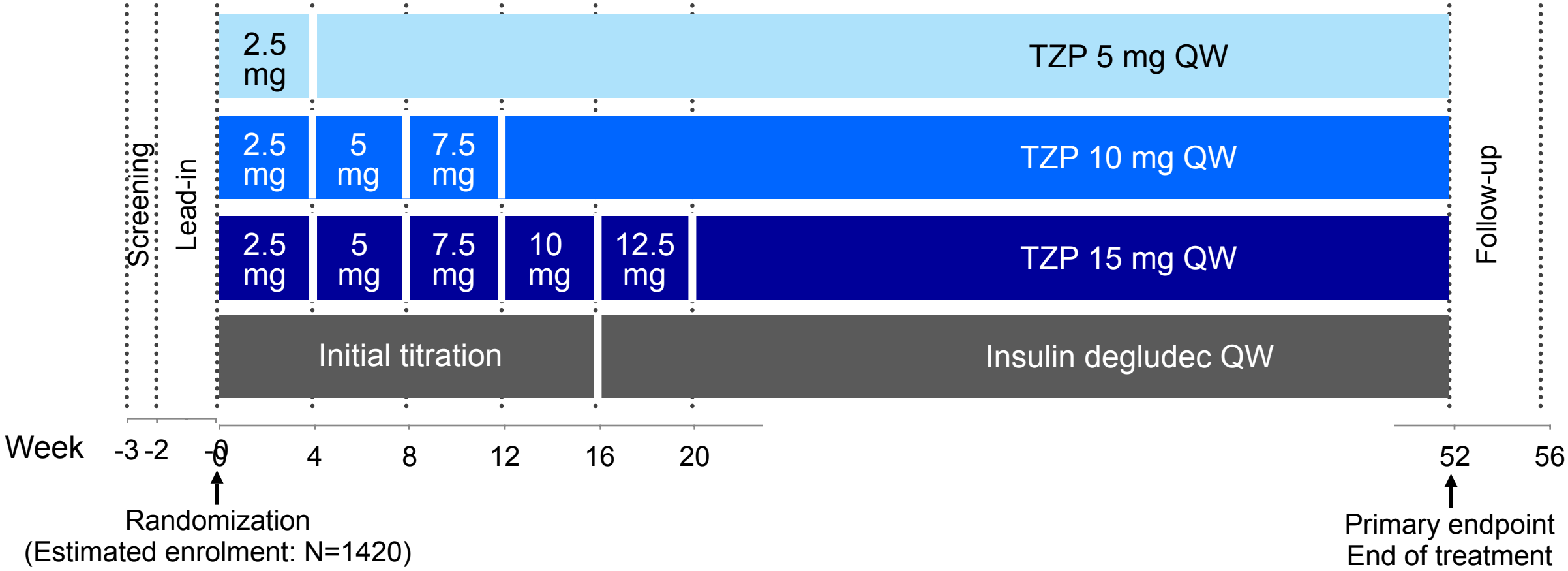
SURPASS-1 Adverse Events

	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg	Placebo
Nausea	11.6%	13.2%	18.2%	6.1%
Diarrhea	11.6%	14.0%	11.6%	7.8%
Vomiting	3.3%	2.5%	5.8%	1.7%
Constipation	5.8%	5%	6.6%	0.9%
Treatment discontinuation*	9.1%	9.9%	21.5%*	14.8%*

No events of severe hypoglycemia or hypoglycemia less than 54 mg/dL were observed in the tirzepatide treatment arms.
*The majority of the discontinuations in the 15 mg and placebo arms were due to reasons other than adverse events (such as concerns due to the coronavirus pandemic and family or work reasons).
SURPASS 1 Press Release December 9 2020 Lilly's tirzepatide significantly reduced A1C and body weight in people with type 2 diabetes | Eli Lilly and Company

SURPASS-3: H2H versus insulin degludec

Open-label study comparing the safety and efficacy of tirzepatide (5, 10, and 15 mg) vs insulin degludec in participants with T2D who have inadequate glycemic control on stable doses of metformin with or without an SGLT-2i (HbA_{1c} ≥7.5% and ≤10.5%)



SURPASS-3. Available at: https://clinicaltrials.gov/ct2/show/NCT03882970. Accessed May 2020

SURPASS 3 Top Line Results – Efficacy Estimand*

	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg	Insulin Degludec
A1c reduction-% Baseline of 8.17	-1.93	-2.20	-2.37	-1.34
Weight reduction-kg Baseline 94.3kg	-7.5 (-8.1%)	-10.7 (-11.4%)	-12.9 (-13.9%)	+2.3 (+2.7%)
Percent of participants achieving A1C <7%	82.4%	89.7%	92.6%	61.3%
Percent of participants achieving A1C <5.7%	25.8%	38.6%	48.4%	5.4%

Mean starting dose of insulin degludec was 10 U/day. Insulin was titrated to target fasting blood glucose < 5.0 mmol/L. Mean dose at 52 weeks was 48.8 U/day.

*Efficacy estimand represents efficacy prior to discontinuation of study drug or initiating rescue therapy for persistent severe hyperglycemia.
All three tirzepatide doses led to statistically significant A1C and body weight reductions from baseline and also reached statistical significance in the percentage of participants who achieved an A1C of less than 7 percent or less than 5.7 percent.
SURPASS 3 Press Release February 17 2021 Tirzepatide significantly reduced A1C and body weight in people with type 2 diabetes in two phase 3 trials from Lilly's SURPASS program | Eli Lilly and Company

SURPASS 3 Top Line Results – Treatment Regimen Estimand*

	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg	Insulin Degludec
A1c reduction from baseline of 8.17%	-1.85%	-2.01%	-2.14%	-1.25%
Weight reduction from baseline of 94.3kg	-7.0kg	-9.6kg	-11.3kg	+1.9kg
Percent of participants achieving A1C <7%	79.2%	81.5%	83.5%	58.0%

Mean starting dose of insulin degludec was 10 U/day. Insulin was titrated to target fasting blood glucose < 5.0 mmol/L. Mean dose at 52 weeks was 48.8 U/day.

*Treatment-regimen estimand represents the efficacy irrespective of adherence to the investigational medicine or introduction of rescue therapy for persistent severe hyperglycemia.
SURPASS 3 Press Release February 17 2021 Tirzepatide significantly reduced A1C and body weight in people with type 2 diabetes in two phase 3 trials from Lilly's SURPASS program | Eli Lilly and Company

SURPASS-3 Adverse Events

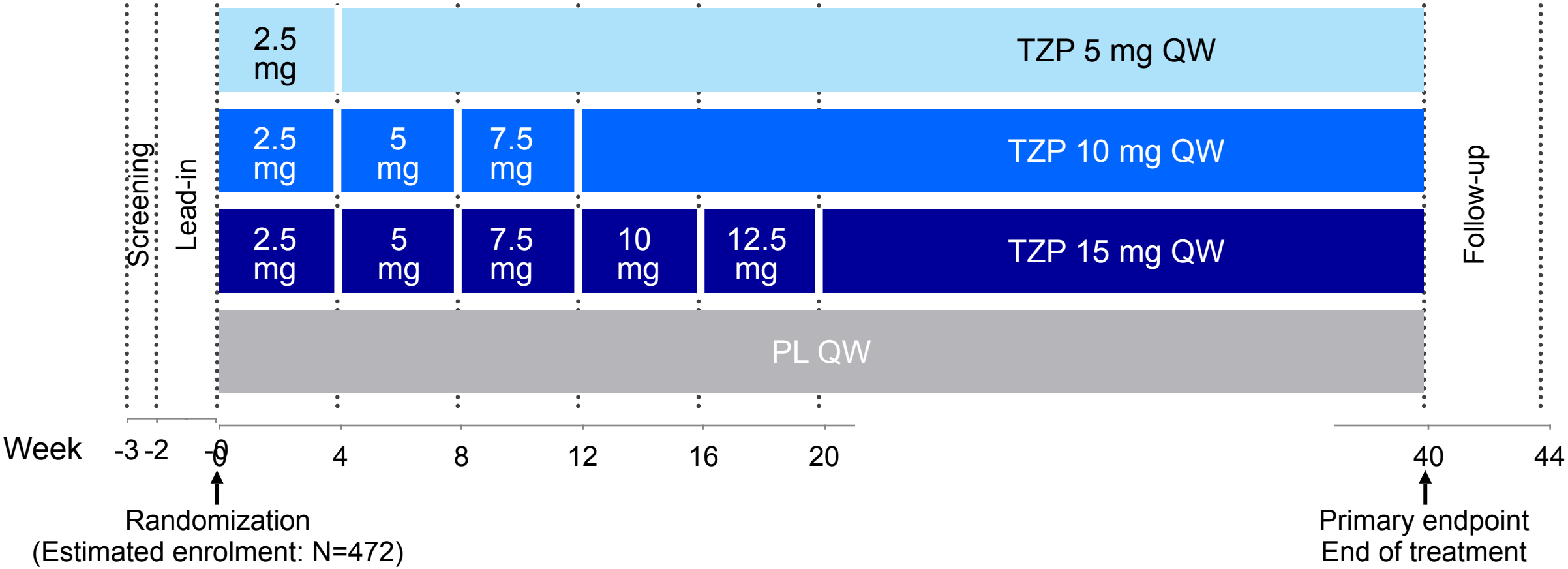
	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg	Insulin Degludec
Nausea	11.5%	22.5%	23.7%	1.7%
Diarrhea	15.4%	16.7%	15.6%	3.9%
Vomiting	5.9%	9.4%	10.0%	1.1%
Hypoglycemia <3 mmol/L	1.4%	1.1%	2.2%	7.3%
Treatment discontinuation due to adverse events	7.2%	9.7%	10.9%	1.4%

Mean starting dose of insulin degludec was 10 U/day. Insulin was titrated to target fasting blood glucose < 5.0 mmol/L. Mean dose at 52 weeks was 48.8 U/day.

SURPASS 3 Press Release February 17 2021 Tirzepatide significantly reduced A1C and body weight in people with type 2 diabetes in two phase 3 trials from Lilly's SURPASS program | Eli Lilly and Company

SURPASS-5: Tirzepatide add-on to insulin glargine

A study to assess the safety and efficacy of tirzepatide (5, 10, and 15 mg) in participants with T2D receiving insulin glargine with or without metformin (HbA_{1c} ≥7.0% and ≤10.5%)



SURPASS-5. Available at: https://clinicaltrials.gov/ct2/show/NCT04039503. Accessed May 2020

SURPASS 5 Top Line Results – Efficacy Estimand*

	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg	Placebo
A1c reduction (%) Baseline 8.31	-2.23	-2.59	-2.59	-0.93
Placebo-adjusted A1C reduction (%)	-1.30	-1.66	-1.66	N/A
Weight reduction kg (%) Baseline 95.2 kg	-6.2 (-6.6%)	-8.2 (-8.9%)	-10.9 (-11.6%)	+1.7 (+1.7%)
Placebo-adjusted weight reduction- kg	-7.9	-9.9	-12.6	N/A
Percent of participants achieving A1C <7%	93.0	97.4	94.0	33.9
Percent of participants achieving A1C <5.7%	26.1	47.8	62.4	2.5

*Efficacy estimand represents efficacy prior to discontinuation of study drug or initiating rescue therapy for persistent severe hyperglycemia.
All three tirzepatide doses led to statistically significant A1C and body weight reductions from baseline and also reached statistical significance in the percentage of participants who achieved an A1C of less than 7 percent or less than 5.7 percent.
Insulin glargine was titrated in all arms with the goal of fasting blood glucose < 5.6 mmol/L. Baseline insuline glargine dose of 37.6 U/day.
SURPASS 5 Press Release February 17 2021 Tirzepatide significantly reduced A1C and body weight in people with type 2 diabetes in two phase 3 trials from Lilly's SURPASS program | Eli Lilly and Company

SURPASS 5 Top Line Results – Treatment Regimen Estimand*

	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg	Placebo
A1c reduction (%) Baseline of 8.31	-2.11	-2.40	-2.34	-0.86
Weight reduction (kg) Baseline- 95.2kg	-5.4	-7.5	-8.8	+1.6
Percent of participants achieving A1C <7%	87.3	89.6	84.7	34.5
Insulin glargine dose (U/day)	37.6	35.7	29.4	58.8

Insulin glargine was titrated in all arms with the goal of fasting blood glucose < 5.6 mmol/L. Baseline insuline glargine dose of 37.6 U/day

*Treatment-regimen estimand represents the efficacy irrespective of adherence to the investigational medicine or introduction of rescue therapy for persistent severe hyperglycemia.

SURPASS 5 Press Release February 17 2021 Tirzepatide significantly reduced A1C and body weight in people with type 2 diabetes in two phase 3 trials from Lilly's SURPASS program | Eli Lilly and Company

SURPASS-5 Adverse Events

	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg	Placebo
Nausea	12.9%	17.6%	18.3%	2.5%
Diarrhea	12.1%	12.6%	20.8%	10.0%
Vomiting	6.9%	7.6%	12.5%	2.5%
Constipation	6.0%	6.7%	6.7%	1.7%
Hypoglycemia <3 mmol/L	15.5%	19.3%	14.2%	12.5%
Treatment discontinuation due to adverse events	6.0%	8.4%	10.8%	2.5%

Insulin glargine was titrated in all arms with the goal of fasting blood glucose < 5.6 mmol/L. Baseline insuline glargine dose of 37.6 U/day

SURPASS 5 Press Release February 17 2021 Tirzepatide significantly reduced A1C and body weight in people with type 2 diabetes in two phase 3 trials from Lilly's SURPASS program | Eli Lilly and Company

SURPASS-1, SURPASS-3, SURPASS-5, and STEP-1 (Efficacy Estimand)

(This side-by-side comparison is to generate discussion only. Between trial comparison is not recommended.)

	T2D												Obesity w/o T2D	
	Tirzepatide Phase 3* [1] (SURPASS-1, N=478, 40 weeks)				Tirzepatide vs Degludec Phase 3*[2] (SURPASS-3, N=1420, 52 weeks)				Tirzepatide add-on to Glargine Phase3* [2] (SURPASS-5, N=472, 40 weeks)				Semaglutide 2.4 mg*[3] (STEP-1, N=1961, 68 weeks)	
	5 mg	10 mg	15 mg	Placebo	5 mg	10 mg	15 mg	Insulin Degludec	5 mg	10 mg	15 mg	Placebo	2.4 mg	Placebo
HbA1c at baseline (%)	7.9				8.17				8.31				5.7	
HbA1c change from baseline (%)	-1.87	-1.89	-2.07	+0.04	-1.96	-2.3	-2.37	-1.34	-2.23	-2.59	-2.59	-0.93	-0.5	-0.16
Percent of participants achieving HbA1c <7%	86.8	91.5	87.9	19.6	82.4	89.7	92.6	61.3	93.0	97.4	94.0	33.9	N/A	N/A
Percent of participants achieving HbA1c <5.7%	33.9	30.5	51.7	0.9	25.8	38.6	48.4	5.4	26.1	47.8	62.4	2.5	N/A	N/A
Mean baseline body weight	85.9 kg				94.3 kg				95.2 kg				105.3# kg	
Body weight reduction	-7.0kg (-7.9%)	-7.8kg (-9.3%)	-9.5kg (-11.0%)	-0.7kg (-0.9%)	-7.5kg (-8.1%)	-10.7 kg (-11.4%)	-12.9 kg (-13.9%)	+2.3 kg (+2.7%)	-6.2kg (-6.6%)	-8.2kg (-8.9%)	-10.9kg (-11.6%)	+1.7kg (+1.7%)	-17.4kg (-16.86%)	-2.7kg (-2.44%)
Nausea (%)	11.6	13.2	18.2	6.1	11.5	22.5	23.7	1.7	12.9	17.6	18.3	2.5	44.2	17.4
Vomiting (%)	3.3	2.5	5.8	7.8	15.4	16.7	15.6	3.9	12.1	12.6	20.8	10.0	24.8	6.6
Diarrhea (%)	11.6	14	11.6	1.7	5.9	9.4	10.0	1.1	6.9	7.6	12.5	2.5	31.5	15.9
D/C due to AE (%)	<7	<7	<7	NR	7.2	9.7	10.9	1.4	6.0	8.4	10.8	2.5	7.0	3.1
D/C due to GI AE (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	4.5	0.8
D/C overall (%)	9.1	9.9	21.5**	14.8**	NR	NR	NR	NR	NR	NR	NR	NR	17.1	22.4

**The majority of the discontinuations in the 15 mg and placebo arms were due to reasons other than adverse events (such as concerns due to the coronavirus pandemic and family or work reasons)

*Results shown are efficacy estimands. D/C = discontinuation N/V/D = nausea, vomiting or diarrhea #Weighted average of the two arms of the study. In SURPASS-3: patients were on background of metformin. NR = not reported AE = adverse events T2D= type 2 diabetes, N/A: not applicable

1- Lilly Press Release SURPASS-1 link
2. Lilly Press Release SURPASS-3 and SURPASS-5 link
3. Wilding et al. NEJM 2021

SURPASS-CVOT Trial Design

SURPASS-CVOT TRIAL DESIGN

- Approximately 12,500 patients with Type 2 Diabetes and confirmed atherosclerotic CV disease

- **Primary Endpoint:** Time to first occurrence of the composite endpoint of CV Death, MI or Stroke

- **Key Secondary Endpoints**
  - Time to all-cause mortality
  - Time to first occurrence of individual components of primary endpoint (CV Death, MI and Stroke)

* As of March 6, 2020
https://clinicaltrials.gov/ct2/show/NCT04255433?term=tirzepatide&draw=2&rank=7

Tirzepatide: Initiating Research in New Indications
Investor Relations Dec 2018

2019

Obesity Phase 3 Initiation

- Weight loss in obese/overweight patients
- Weight loss in obese/overweight T2DM patients
- Maximizing weight loss
- Maintenance of weight loss

Obesity is increasing in prevalence and is associated with significant co-morbidities and cardiovascular complications (Type 2 Diabetes, Cardiovascular Disease)

2019

Nonalcoholic Steatohepatitis Phase 2 Initiation

- NASH biopsy study

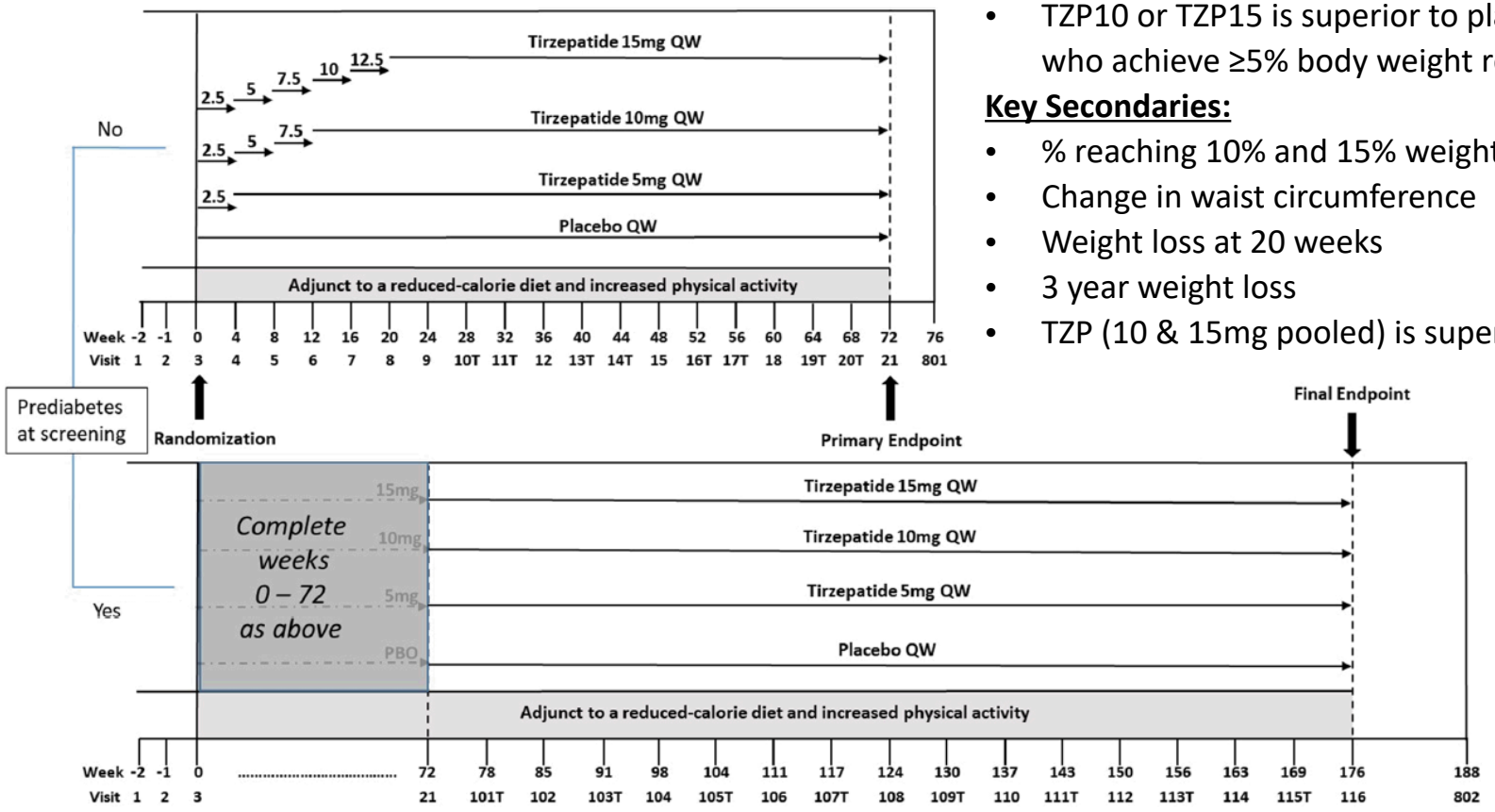
NASH is increasing in prevalence and associated with risk of cirrhosis, liver transplantation, and cardiovascular complications

https://investor.lilly.com/webcasts-and-presentations

SURMOUNT Obesity Program

Tirzepatide: SURMOUNT-1 trial

N=2,400



Primary Objective:

- TZP10 or TZP15 is superior to placebo for body weight change and subjects who achieve ≥5% body weight reduction (at week 72)

Key Secondaries:

- % reaching 10% and 15% weight loss
- Change in waist circumference
- Weight loss at 20 weeks
- 3 year weight loss
- TZP (10 & 15mg pooled) is superior to placebo for diabetes prevention

Inclusion Criteria:

- Male or female, age ≥18 years
- BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with ≥1 weight related comorbidity
- History of at least one self-reported unsuccessful dietary effort to lose body weight

Exclusion Criteria:

- Diabetes mellitus
- Use of approved weight lowering pharmacotherapy
- A self-reported change in body weight >5kg, 3 months before screening

TZP = Tirzepatide BMI= Body mass index

NCT04184622

Tirzepatide: SURMOUNT-2 trial

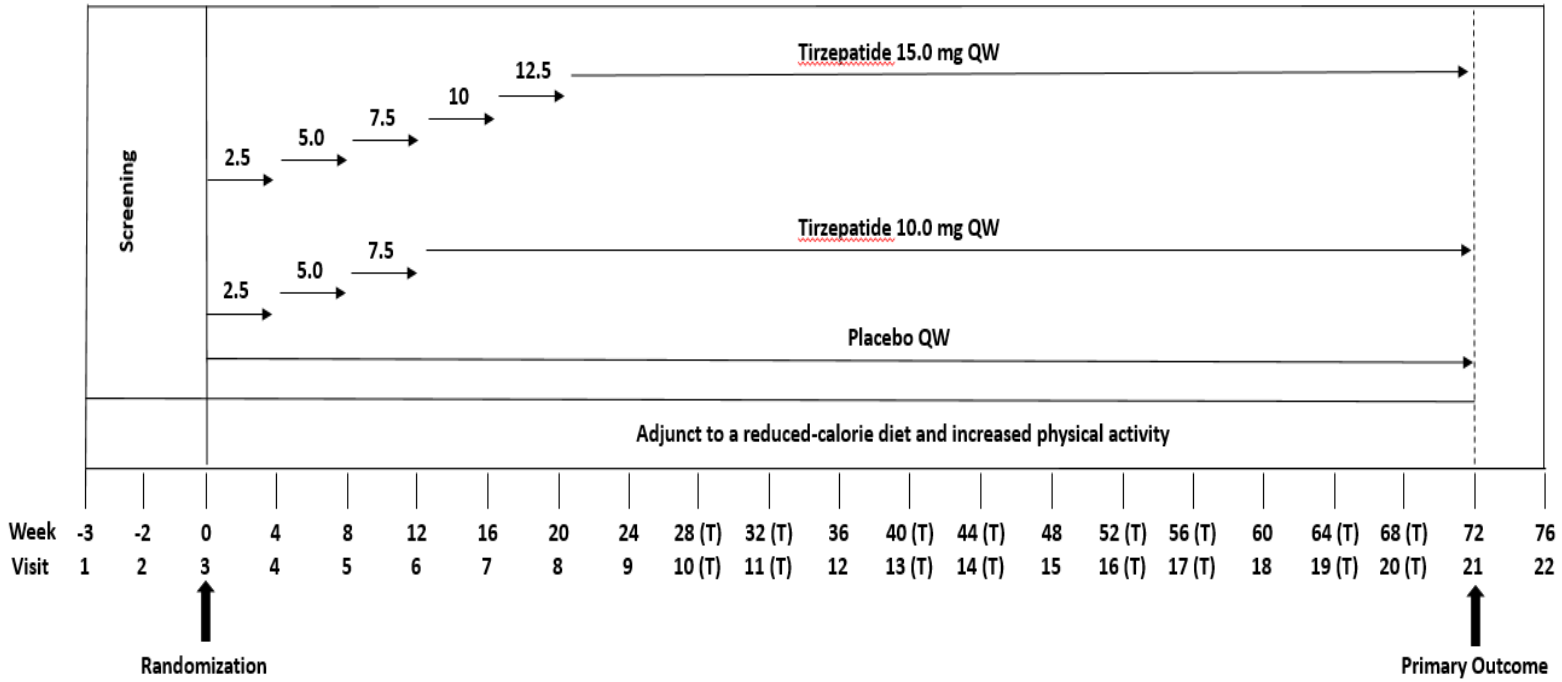
N=900

Primary Objective:

- TZP10 or TZP15 is superior to placebo for Body Weight Change and Subjects Who Achieve ≥5% Body Weight Reduction

Key Secondaries:

- % reaching 10% and 15% weight loss
- Mean change in A1c
- % to A1c <7%
- Change in waist circumference



Inclusion Criteria:

- Type 2 diabetes
- Male or female, age ≥18 years
- BMI ≥ 27 kg/m^2 with T2DM (A1c 7-10%), treated with 0-3 oral agents
- History of at least one self-reported unsuccessful dietary effort to lose body weight

Exclusion Criteria:

- Insulin or other injectable treatment for T2DM
- Use of approved weight lowering pharmacotherapy
- A self-reported change in body weight >5% 3 months before screening

TZP = Tirzepatide BMI= Body mass index T2DM= Type 2 diabetes mellitus A1c= Glycated hemoglobin

NCT04657003

Tirzepatide: SURMOUNT-3 trial

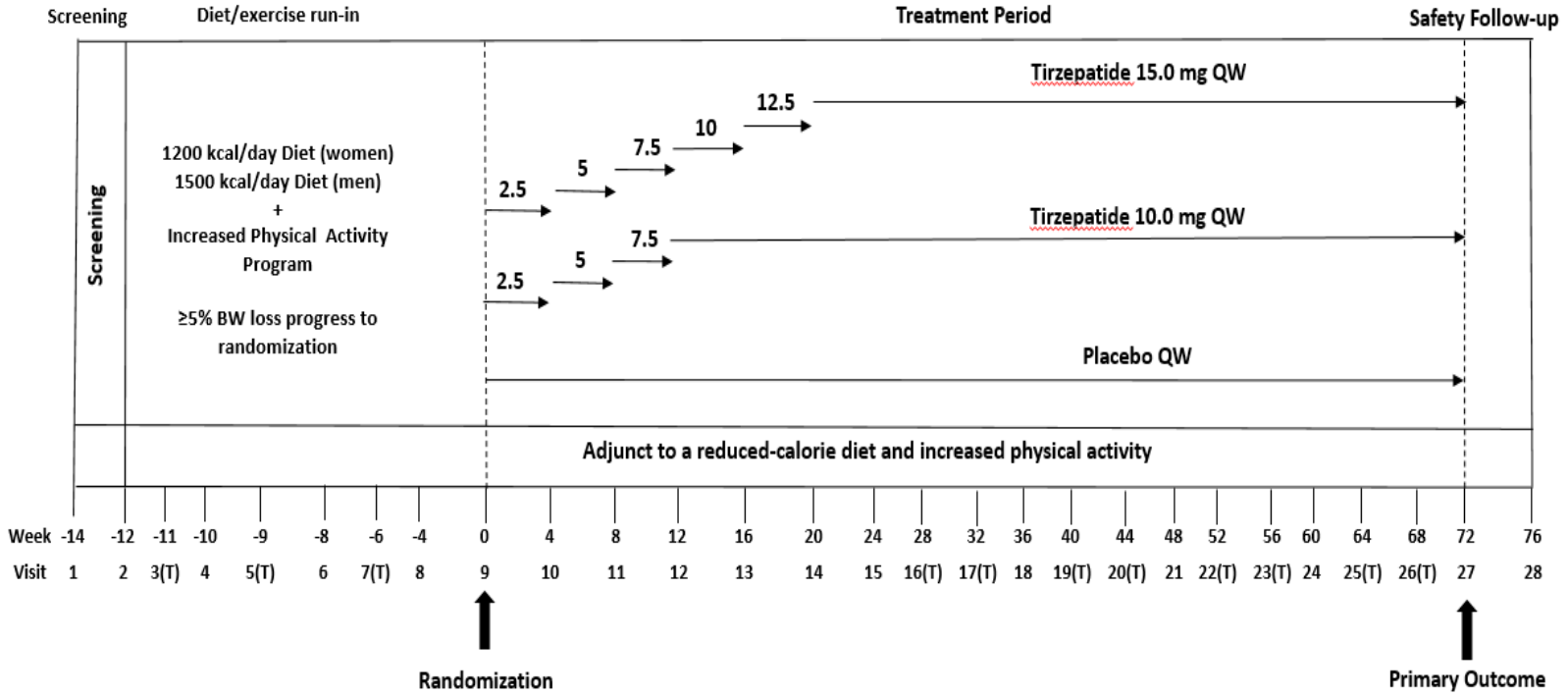
N=800

Primary Objective:

- TZP10 or TZP15 is superior to placebo for body weight change and subjects who achieve ≥5% body weight reduction

Key Secondaries:

- % maintaining ≥80% of the body weight lost during intensive lifestyle program
- % reaching 10% and 15% weight loss
- Changes in waist circumference
- Changes in blood pressure



TZP = Tirzepatide BMI= Body mass index

NCT04657016

Inclusion Criteria:

- Male or female, age ≥18 years
- BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with ≥1 weight related comorbidity
- History of at least one self-reported unsuccessful dietary effort to lose body weight

Exclusion Criteria:

- Diabetes mellitus
- Use of approved weight lowering pharmacotherapy
- A self-reported change in body weight >5kg, 3 months before screening

Randomization Criteria:

- Achieve ≥5% weight loss with intensive lifestyle change in study period I

Tirzepatide: SURMOUNT-4 trial

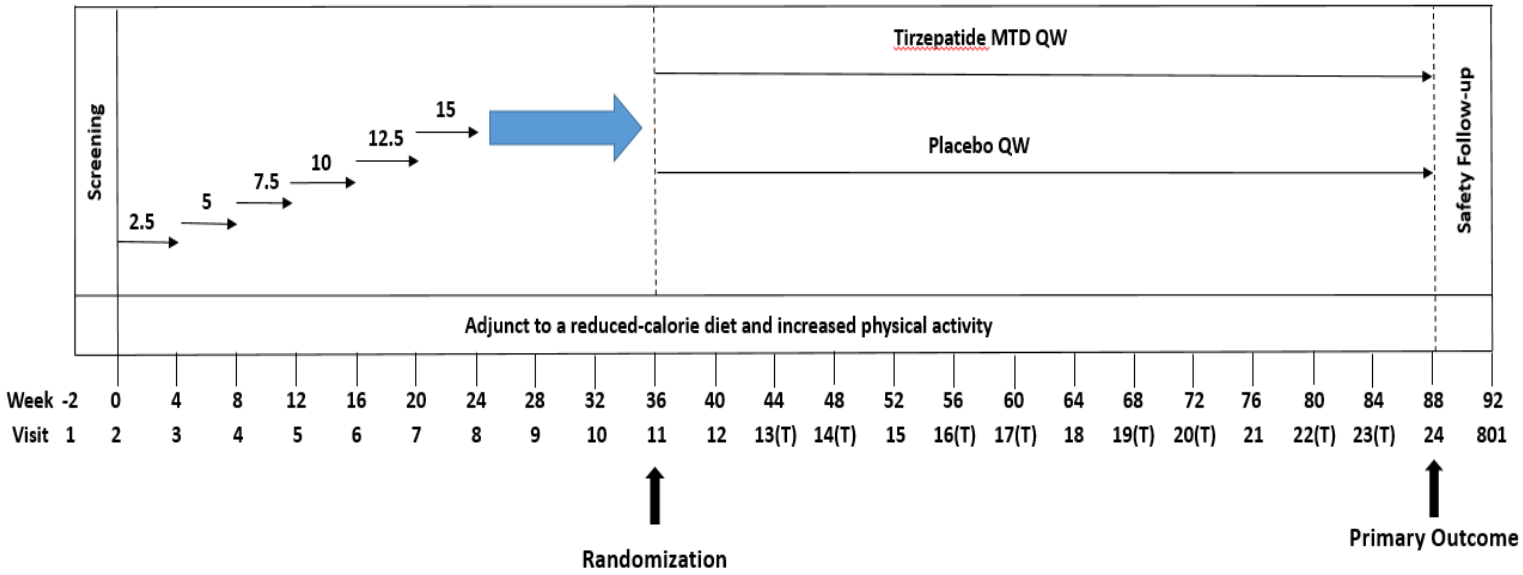
N=750

Primary Objective:

- % weight change from Randomization to week 88 for maximal tolerated dose (MTD) TZP vs placebo

Key Secondaries:

- Mean change in body weight from randomization to week 88
- Change in waist circumference
- % who achieve ≥10% body weight reduction
- % who maintain ≥80% of the body weight lost during the open-label period



*maximal tolerated dose (10 vs 15 mg)

**study design consideration: 36 week randomization to optimize before discontinuation

Inclusion Criteria:

- Male or female, age ≥18 years
- BMI ≥ 30 kg/m² or ≥ 27 kg/m² with ≥1 weight related comorbidity
- History of at least one self-reported unsuccessful dietary effort to lose body weight

Exclusion Criteria:

- Diabetes mellitus
- Use of approved weight lowering pharmacotherapy
- A self-reported change in body weight >5kg, 3 months before screening

Randomization Criteria:

- Achieve MTD of at least TZP 10 mg in dose escalation period

TZP = Tirzepatide BMI= Body mass index MTD= Maximum tolerated dose

NCT04660643

SYNERGY-NASH Phase 2 Study

SYNERGY-NASH (Phase 2)

A Study of Tirzepatide (LY3298176) in Participants With Nonalcoholic Steatohepatitis (NASH) (SYNERGY-NASH)

- N=196
- 5 mg, 10mg and 15 mg being tested vs placebo

- Actual Study Start Date : November 19, 2019
- Estimated Primary Completion Date*: March 21, 2022
- Estimated Study Completion Date*: March 21, 2022

Primary Outcome Measure

- Percentage of Participants with Absence of NASH with no Worsening of Fibrosis on Liver Histology (52 weeks)

* As of February 12 2020
https://clinicaltrials.gov/ct2/show/NCT04166773

SYNERGY-NASH (Phase 2)

Secondary Outcomes include:

- Percentage of Participants with ≥1 Point Decrease in Fibrosis Stage with No Worsening of NASH on Liver Histology (52 weeks)
- Percentage of Participants with ≥1 Point Increase in Fibrosis Stage on Liver Histology (52 weeks)
- Percentage of Participants that Achieve a ≥2 Point Decrease in NAFLD (non-alcoholic fatty liver disease) Activity Score (NAS) on Liver Histology, with ≥1 Point Reduction in at Least 2 NAS Components (52 weeks)
- Mean Absolute Change from Baseline in Liver Fat Content by Magnetic Resonance Imaging - Proton Density Fat Fraction (MRI-PDFF) (baseline, 52 weeks)
- Mean Change from Baseline in Body Weight (baseline, 52 weeks)

https://clinicaltrials.gov/ct2/show/NCT04166773

SYNERGY-NASH (Phase 2)
Major Inclusion/Exclusion Criteria

Inclusion	Exclusion
Body mass index (BMI) ≥27 kilograms per square meter (kg/m²) and ≤50 kg/m² with stable body weight for at least 3 months	Known or suspected alcohol abuse (>14 units/week for women and >21 units/week for men) or active substance abuse
Participants with or without type 2 diabetes mellitus (T2DM) - If with T2DM, hemoglobin A1c (HbA1c) ≤9.5%	Cirrhosis or other forms of liver disease
Participants must be willing to undergo baseline and endpoint liver biopsies	Heart attack, stroke, or hospitalization for congestive heart failure in the past 6 months
Histologic diagnosis of NASH with stage 2 or 3 fibrosis by liver biopsy	Active cancer within the last 5 years
	Participants must not have uncontrolled high blood pressure
	Renal impairment with estimated glomerular filtration rate (eGFR) <30 milliliters/minute/1.73m²; for participants on metformin, eGFR <45 mL/min/1.73m²
	Diagnosis of type 1 diabetes
	History of pancreatitis (acute or chronic)
	Calcitonin ≥35 nanograms per liter
	Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma (family is defined as a first degree relative
	Be pregnant, breast-feeding, or intend to become pregnant or of childbearing potential and not using adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice)

https://clinicaltrials.gov/ct2/show/NCT04166773