Tirzepatide (MOUNJARO) Injection
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist.

Indication(s) Under Review in This Document

- Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Dosage Form(s) Under Review

- Available in (4) pre-filled single-dose pens in the following strengths: 2.5mg, 5mg, 7.5mg, 10mg, 12.5mg, 15mg
- The recommended starting dosage is 2.5 mg injected subcutaneously once weekly. After 4 weeks, increase to 5 mg injected subcutaneously once weekly. If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose. The maximum dosage is 15 mg subcutaneously once weekly.
- Administer once weekly at any time of day, with or without meals. Inject subcutaneously in the abdomen, thigh, or upper arm.

Clinical Evidence Summary

Efficacy Considerations

Included in this review are the phase 3 randomized controlled trials SURPASS 1-6. There is one placebo-controlled trial comparing tirzepatide monotherapy to placebo and 4 trials comparing tirzepatide to active controls (semaglutide, insulin degludec, insulin glargine, insulin lispro) as add-on therapy to metformin alone, metformin +/- SGLT2 inhibitor, insulin glargine +/- metformin therapy, and 1-3 oral agents (metformin, SGLT2 inhibitors, sulfonylureas)

At the time of this writing, results for SURPASS-6 comparing tirzepatide to insulin lispro as add-on to insulin glargine +/- metformin were not available.

In the trials that had insulin as a comparator, the dose was started at 10 units per day and titrated according to the treat-to-target algorithm.

Key inclusion criteria: Type 2 diabetes, A1C 7.5% to 10.5% (7.5% to 9.5% in SURPASS-1), BMI of 25 kg/m² or greater (23 or greater in SURPASS-1 and 5), stable weight (no change outside of 5%) during the previous 3 months, agree to not initiate a diet or exercise program during the study with the intent of reducing bodyweight other than the lifestyle and dietary measures for diabetes treatment.

SURPASS-4 was studied in patients who were at increased risk of cardiovascular events, defined as known coronary, peripheral arterial, or cerebrovascular disease, or aged 50 years or older with either history of chronic kidney disease and an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1·73 m² or history of congestive heart failure (New York Heart Association Class II or III).

Key exclusion criteria: Type 1 diabetes; history of chronic or acute pancreatitis any time prior to study; history of proliferative diabetic retinopathy, diabetic maculopathy, or non-proliferative diabetic retinopathy that requires acute treatment; estimated glomerular filtration rate of less than 45 mL/min per 1·73 m² (less than 30 in SURPASS-1; for studies using metformin eGFR limits based on labeling); clinically significant gastric emptying abnormality; history of New York Heart Association Functional Classification IV CHF (SURPASS-3 and 5 also excluded NYHA III); treatment with drugs that promote weight loss within 3 months prior to study; acute or chronic hepatitis and other liver diseases ALT level greater than 3.0 times the upper limit of normal (ULN) for the reference range (patients with nonalcoholic fatty liver disease are allowed to participate if ALT is less than or equal to 3.0 times ULN; acute myocardial infarction, stroke, or hospitalization due to congestive heart failure 2 months prior to visit 1, family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. (Refer to supplementary appendix of published trials for complete list of eligibility criteria).

Demographics and baseline information: mean age 58 years, 4% >/= 75 years, 58% male, 65% White, 24% Asian, 7% American Indian or Alaska Native, and 3% Black or African American; 38% Hispanic or Latino, mean duration of diabetes 9.1 years, mean HbA1c 8.3%, 15% had retinopathy. At baseline, eGFR was ≥90 mL/min/1.73 m2 in 52%, 60 to 90 mL/min/1.73 m2 in 40%, 45 to 60 mL/min/1.73 m2 in 6%, and 30 to 45 mL/min/1.73 m2 in 1% of patients.

Across the SURPASS 1-5 trials, average decrease in A1C ranged from 1.9% to 2.2% (5mg), 1.9% to 2.4% (10mg), and 2.1% to 2.6% (15mg). See **Table 1** for select glycemic outcomes.

Table 1: Glycemic Efficacy Results from Phase 3 Clinical Trials

Study	Concom-itant Tx	Tx Arms	N	BL A1C (%)	A1C (%)	%A1C ≤7%	BL FPG mg/dL	FPG mg/dL	Mean daily glucose (mg/dL)¶	2-hour PPG (mg/dL)¶	Rescue tx (%)
Rosenstock SUPASS-1 40 weeks	None	TZP5 TZP10 TZP15 PBO	121 121 121 115	8.0	-1.87* -1.89* -2.07* 0.04	87* 92* 88* 20	154	-44 -46 -49 13	-56 -54 -55 -8	-65 -61 -65 -11	2 3 2 25
Frias SURPASS-2 40 weeks	MET	TZP5 TZP10 TZP15 SEM1	470 469 470 469	8.3	-2.01* -2.24* -2.30* -1.86	82 86* 86* 79	173	-56 -62 -63 -49	-65 -71 -74 -61	-72 -78 -82 -67	1.3-1.5 (TZP) 2.8 (SEM)
Ludvik SURPASS-3 52 weeks	MET alone (68%) or MET± SGLT2i (32%)	TZP5 TZP10 TZP15 IDEG^	358 360 359 360	8.2	-1.93* -2.20* -2.37* -1.34	82* 90* 93* 61	170	-48 -55 -59 -56	-53* -60* -61* -48	-60* -67* -68* -50	
Del Prato SURPASS-4 52-104 weeks§	1-3 OADs (MET 95%, SU 54%, SGLT2i 25%)	TZP5 TZP10 TZP15 IGLA‡	329 328 338 1000	8.5	-2.24* -2.43* -2.58* -1.44	81* 88* 91* 51	171	-50 -55 -59* -51	-58 -61 -66 -46	-67 -69 -74 -49	0.3-0.9 (TZP) 0.5 (GLA)
Dahl SURPASS-5† 40 weeks	IGLA±MET (MET 83%)	TZP5 TZP10 TZP15 PBO	116 119 120 120	8.3	-2.11* -2.40* -2.34* -0.86	87* 90* 85* 35	162	-58* -64* -63* -39	-67* -72* -74* -39	-77* -82* -87* -41	Results?

Abbreviations: BL=baseline; FPG=fasting plasma glucose; IDEG=insulin degludec; IGLA=insulin glargine; ILIS=insulin lispro MET=metformin; OAD=oral antiglycemic drugs; PBO=placebo; PPG=postprandial glucose; SEM=semaglutide; SGLT2i=sodium glucose co-transporter-2 inhibitor; SU=sulfonylurea; TZP=tirzepatide

*Statistically significant vs comparator

¶Based on 7-point self-monitoring of blood glucose

^SURPASS-3: mean dose of insulin degludec 49U/day
‡SURPASS-4: mean dose of insulin glargine 43U/day
†SURPASS-5: Baseline glargine dose 34U (0.36U/kg); change in glargine dose from BL +4.4U (TZP5); +2.7U (TZP10); -3.8U (TZP15); +25.1 (PBO)
§Primary and secondary endpoints were measured at 52 weeks. This trial had a variable treatment period that included up to an additional 52 weeks to collect long-term safety data and achieve a predefined number of MACE-4. Not all patients were treated for 104 weeks

Weight

Across the SURPASS 1-5 trials, average weight loss ranged from 5.4 to 7.6kg (5mg dose), 7.5 to 10.7 (10mg dose), and 8.8 to 12.9kg (15mg dose). See **Table 2** for select weight outcomes.

Table 2: Weight Loss Results from Phase 3 Clinical Trials

Study	Background Meds	Tx Arms	N	BL weight (kg)	Weight (kg)	WL >=5%	WL >=10%	BMI kg/m²	Waist circ (cm)
SUPASS-1 40 weeks	None	TZP5	121	86	-7.0*	67*	31*	-2.6	-5.7
		TZP10	121		-7.8*	78*	40*	-2.9	-6.9
		TZP15	121		-9.5*	77*	47*	-3.6	-7.2
		PBO	115		-0.7	14	1	-0.2	-2.0
SURPASS-2 40 weeks	MET	TZP5	470	94	-7.6*	65	34	-2.9	-6.9
		TZP10	469		-9.3*	76	47	-3.8	-9.6
		TZP15	470		-11.2*	80	57	-4.6	-9.9
		SEM1	469		-5.7	54	24	-2.3	-5.6
SURPASS-3 52 weeks	MET± SGLT2i	TZP5	358	94	-7.5*	66*	37*	-2.7 to -4.6 (TZP)	-7.1 to -10.9 (TZP)
		TZP10	360		-10.7*	84*	56*		
		TZP15	359		-12.9*	88*	69*		
		IDEG^	360		+2.3	6	3	0.9	0.6
SURPASS-4 52-104 weeks	1-3 OADs (MET, SU, SGLT2i)	TZP5	329	90	-6.4	63*	36*	-2.6	
		TZP10	328		-8.9	78*	53*	-3.7	
		TZP15	338		-10.6	85*	66*	-4.0	
		IGLA‡	1000		+1.7	8	2	0.9	
SURPASS-5 40 weeks**	IGLA±MET	TZP5	116	95	-5.4*	48	21	-2.2	-3.8
		TZP10	119		-7.5*	58	42	-2.9	-7.4
		TZP15	120		-8.8*	72	41	-3.8	-8.9
		PBO	120		+1.6	6	1	0.6	1.0

Abbreviations: BL=baseline; BMI=body mass index; IDEG=insulin degludec; IGLA=insulin glargine; ILIS=insulin lispro MET=metformin; OAD=oral antiglycemic drugs; PBO=placebo; SEM=semaglutide; SGLT2i=sodium glucose co-transporter-2 inhibitor; SU=sulfonylurea; TZP=tirzepatide; WL=weight loss
Composite for SURPASS-2 A1C≤6.5%, ≥10% weight loss, and w/o BG <54mg/dL or significant hypo event (32.1%, 50.8%, 60.1%, 21.9%)
Composite for SURPAS-3 A1C≤6.5%, w/o weight gain, and w/o BG <54mg/dL or significant hypo event (68.9%, 80.7%, 86%, 11.8%)

Cardiovascular Outcomes

- SURPASS-CVOT is a large cardiovascular outcomes trial (n=12,500) comparing tirzepatide to dulaglutide 1.5 mg weekly as add-on therapy to usual medications in patients with T2DM and established atherosclerotic cardiovascular disease. The trial is expected to run for approximately 4.5 years. Primary outcome completion date is expected in October 2024.

- Cardiovascular safety was assessed in SURPASS-4 which was conducted in patients who were at increased risk for CV events. Eighty-seven percent had a history of CVD (documented CAD 44%, MI 32%, coronary revascularization 32%, hospitalization for UA 8%, hospitalization for HF 7%, stroke 12%, TIA 5%, PAD 30%. Baseline medications included: blood pressure lowering meds 93% (ACEI/ARB 78%, BB 41.5%, CCB 15%), lipid lowering medications 82% (statin 77.5%, fibrates 12%), and antiplatelet medications 70%.

  The primary outcome was composite of CV death, MI, stroke, and hospitalization for unstable angina (MACE-4). Also analyzed were the individual components of MACE-4, all deaths, coronary interventions, TIA, and hHF. The trial ended when all patients reached 52 weeks, at least 300 tirzepatide-treated patients reached 78 weeks, and approximately 110 patients had at least one positively adjudicated MACE-4 event.

At study conclusion (median study duration 85 weeks), 109 patients had experienced a MACE-4 event (47 tirzepatide and 62 insulin glargine). There was no overall increased risk of cardiovascular events for tirzepatide versus insulin glargine, hazard ratio of 0.74 (95% CI 0.51–1.08). Results shown in **Table 3.**

Other Outcomes

Tirzepatide can reduce triglycerides, LDL-C, total cholesterol, and increase HDL-C. See Appendix 2 for results.

Table 3: SURPASS-4 and Cardiovascular Safety

Study	TZP5 n(%)	TZP10 n(%)	TZP15 n(%)	All TZP n(%); E/100PY	IGLA n(%); E/100PY	Hazard Ratio [95%CI]
n	329	328	338	995	1000	
MACE-4	19 (6)	17 (5)	11 (3)	47 (5); 2.97	62 (6); 3.99	0.74 [0.51–1.08]
CV death	10 (3)	1 (<1)	5 (2)	16 (2); 1.01	21 (2); 1.35	
MI	7 (2)	9 (3)	3 (<1)	19 (2); 1.20	26 (3); 1.67	
Stroke	5 (2)	5 (2)	1 (<1)	11 (1); 0.25	13 (1); 0.51	
Hospitalization for UA	0	2 (<1)	2 (<1)	4 (<1); 0.70	8(<1); 0.84	
All deaths	15 (5)	2 (<1)	8 (2)	25 (3); 1.58	35(4); 2.25	0.70 [0.42-1.17]
CV death	4 (1)	0	2 (<1)	6 (<1); 0.38	9 (<1); 0.58	
Undetermined^	6 (2)	1 (<1)	3 (<1)	10 (1); 0.63	12 (1); 0.77	
Non-CV	5 (2)	1 (<1)	3 (<1)	9 (<1); 0.57	14 (1); 0.90	
Coronary Interventions	10 (3)	11 (3)	8 (2)	29 (3); 1.83	37 (4); 2.38	
TIA	0	2 (<1)	1 (<1)	3 (<1); 0.19	0	
Hospitalization for HF	1 (<1)	1 (<1)	2 (<1)	4 (<1); 0.25	6 (<1); 0.39	

CV=cardiovascular, HF=heart failure, MI=myocardial infarction, TIA=transient ischemic attack, UA=unstable angina
^Undetermined deaths were considered as CV for determining MACE outcomes

- A meta-analysis was conducted analyzing adjudicated major adverse CV events (composite of CV death, MI, stroke, and hospitalization for unstable angina) across the SURPASS clinical program. The hazard ratio for tirzepatide versus comparators was 0.81 (97.85% CI, 0.52-1.26). Most of the events came from SURPASS-4 which was conducted in patients that were at increased risk for cardiovascular events.

Safety Considerations

- **Boxed warnings:**
  - Tirzepatide causes thyroid C-cell tumors in rats. It is unknown whether tirzepatide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined.
  - Tirzepatide is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors.
- **Contraindications:**
  - Personal or family history of MTC or in patients with MEN 2.
  - Known serious hypersensitivity to tirzepatide or any of the excipients in tirzepatide
- **Other warnings / precautions**:
  - Pancreatitis: Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected.
  - Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin: Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing dose of insulin secretagogue or insulin may be necessary.
  - Hypersensitivity Reactions: Hypersensitivity reactions have been reported. Discontinue tirzepatide if suspected.
  - Acute Kidney Injury: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.

- Severe Gastrointestinal Disease: Use may be associated with gastrointestinal adverse reactions, sometimes severe. Has not been studied in patients with severe gastrointestinal disease and is not recommended in these patients.
- Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy: Has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Monitor patients with a history of diabetic retinopathy for progression.
- Acute Gallbladder Disease: Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow-up are indicated.

- **Adverse reactions**
  - **Common** The most common adverse reactions, reported in ≥5% of patients treated with tirzepatide are nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain.
  - Refer to **Appendix 1** for results by study for serious adverse events, deaths, discontinuations due to adverse events, GI-related adverse events, hypoglycemia, injection site reactions, pancreatitis, cholelithiasis, and hypersensitivity reactions
- **Other Safety Outcomes**
  - Pooled data from placebo-controlled trials showed that tirzepatide had a mean increase from baseline in serum pancreatic amylase and lipase concentrations by 33% to 38% and 31% to 42% respectively. Placebo-treated patients had a mean increase from baseline in pancreatic amylase of 4% and no changes in lipase. The clinical significance of elevations in lipase or amylase with tirzepatide is unknown in the absence of other signs and symptoms of pancreatitis.
  - Treatment with tirzepatide resulted in mean decreases in systolic and diastolic blood pressure and increases in mean pulse rate. **See Appendix 2**

Other Considerations

- Liver fat content (LFC) and abdominal adipose tissue was evaluated in a substudy of the SURPASS-3 trial. In addition to the main study inclusion criteria, substudy participants had a fatty liver index of at least 60. Participants (n=296) had an MRI scan and were randomized to tirzepatide 5mg, 10mg, 15mg, or insulin degludec as previously described.

  The primary efficacy endpoint was the change from baseline in LFC (as measured by MRI-proton density fat fraction) at week 52 using pooled data from the tirzepatide 10 mg and 15 mg groups versus insulin degludec. Mean baseline LFC was 15.71%. Reduction in LFC was -8.09% for and -3.38% for the pooled tirzepatide and degludec groups respectively (TD -4.7% [95% CI -6.72 to -2.70; p<0.0001]).

- Following administration of a combined oral contraceptive (0.035 mg ethinyl estradiol and 0.25 mg norgestimate) in the presence of a single dose of tirzepatide 5 mg, mean Cmax of ethinyl estradiol, norgestimate, and norelgestromin was reduced by 59%,66%, and 55%, while mean AUC was reduced by 20%, 21%, and 23%, respectively. A delay in tmax of 2.5 to 4.5 hours was observed. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with tirzepatide. Hormonal contraceptives that are not administered orally should not be affected.

- Available data with tirzepatide use in pregnant women are insufficient to evaluate for a drug-related risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy. Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy. Tirzepatide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- There are no data on the presence of tirzepatide in animal or human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tirzepatide and any potential adverse effects on the breastfed infant from tirzepatide or from the underlying maternal condition.

Other Therapeutic Options

Select alternative treatments used to treat type 2 diabetes are compared in table 3 below.

Table 3 Formulary Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
Tirzepatide	TBD	TBD	• Once weekly injection • Dose-related A1C lowering 1.9%-2.6% • Weight loss • Low risk of hypoglycemia • CVOT trial ongoing; CV safety shown in SURPASS-4 • Very costly
Semaglutide	PA-F	• Second-line after metformin for those with CVD/CKD if not a good candidate for EMPA • Third-line for all others who need additional glucose control	• Once-weekly injection • A1C lowering 1-1.9%; semaglutide 2mg -2.1% • Weight loss • Low risk of hypoglycemia • CV and renal benefits • High cost
Empagliflozin	Formulary	Second-line after metformin	• Once daily oral administration • A1C lowering </= 1% • Weight loss • Low risk of hypoglycemia • Cardiovascular, HF, and renal benefits • Less costly than GLP-1 agonists
Insulin (NPH, glargine 100U, detemir, glargine 300U, degludec, regular, apart)	Glargine 300U and degludec PA-F	Formulary insulin can be considered any time	• Injectable, titratable, • Risk of hypoglycemia, weight gain, • Low to moderate cost (excluding concentrated insulins)

Projected Place in Therapy

Tirzepatide may be considered as an intensification option for patients with type 2 diabetes treated with semaglutide 1mg or 2mg in need of additional glycemic control. Before considering tirzepatide, current diabetes therapy, including diet and exercise, should be optimized as appropriate and adherence to therapy confirmed. If not already using, consider adding empagliflozin or insulin if appropriate.

Appendix 1

Study	Concomitant Tx	Tx Arms	N	≥1 SAE (%)	Deaths N (%)	D/C due to AE (%)	All GI AEs (%)	N/V/D (%)	Hypo <70mg/dL (%)	Hypo<54 mg/dL (%)	Inj site rxs (%)	Adj pancreatitis (n)	Chole-lithiasis N(%)	DR (%)	Hyper-sensitivity rxs %
Rosenstock SUPASS-1 40 weeks	None	TZP5	121	4	0	3	38	12/3/12	6	0	3	None	1 (1.0)	0	3 (2.0)
		TZP10	121	2	0	5	41	13/2/14	7	0	3		0	0	2 (2.0)
		TZP15	121	1	0	7	41	18/6/12	7	0	2		0	0	1 (1.0)
		PBO	115	3	1(<1%)	3	19	6/2/8	1	1	0		0	0	1 (1.0)
Frias SURPASS-2 40 weeks	MET	TZP5	470	7	4 (0.9)	6	40	17/6/13	N/A	0.6	1.9	0	4 (0.9)	0	1.9
		TZP10	469	5.3	4 (0.9)	8.5	46	19/9/16		0.2	2.8	2	4 (0.9)	2 (0.4)	2.8
		TZP15	470	5.7	4 (0.9)	8.5	45	22/10/14		1.7	4.5	2	4 (0.9)	0	1.7
		SEM1	469	2.8	1 (0.2)	4.1	41	18/8/12		0.4	0.2	3	2 (0.4)	0	2.3
Ludvik SURPASS-3 52 weeks	MET (68%) MET+SGLT2i (32%)	TZP5	358	8	1(<1%)	7	NR	12/6/15	8	1	<1	None	2 (1.0)	2 (1.0)	3
		TZP10	360	6	2(1%)	10		23/9/17	14	1	2		1 (<1)	0	3
		TZP15	359	7	1(<1%)	11		24/10/16	14	2	2		1 (<1)	1 (<1)	3
		IDEG^	360	6	1(<1%)	1		2/1/4	48	7	2		0	0	1
SURPASS-4	1-3 OADs (MET, SGLT2i, SU)	TZP5		15	15 (5)	11		12/5/13	34*	9*	2% (TZP)	<1	<1	2<1	4% (TZP)
		TZP10		17	2 (<1)	9		16/8/20	33*	6*	2% (GLA)	<1	<1	1<1	
		TZP15		12	8 (2)	11		23/9/22	38*	8*		<1	<1	1<1	2% (GLA)
		IGLA		19	35 (4)	5		2/2/4	64*	19*		<1	<1	1<1	
SURPASS-5	IGLA±MET	TZP5	116	7.8	None	6		13/7/12	60	15	3.4	None	0.9	None	6.9
		TZP10	119	10.9		8.4		18/8/13	63	19	2.5		0		2.5
		TZP15	120	7.5		10.8		18/12/21	60	14	6.7		0		5.0
		PBO	120	8.3		2.5		2/2/10	61	12	0.8		0		2.5

*Hypoglycemia according to SU use in Surpass-4: <70mg/dL (on SU 52%,50%,55%,70%) no SU (10%,12%,18%,57%); <54mg/dL (on SU 14%,10%,13%,22%) no SU (2%,1%,3%,16%)

Abbreviations: GI=gastrointestinal=IDEG=insulin degludec; IGLA=insulin glargine; MET=metformin; N/V/D=nausea/vomiting/diarrhea; OAD=oral antidiabetic drugs; PBO=placebo; rxs=reactions; SEM=semaglutide; SAE=serious adverse event; SGLT2i= sodium-glucose cotransporter-2 inhibitor; SU=sulfonylurea; TZP=tirzepatide

Appendix 2

	Concomitant Tx	Tx Arms	N	BL SBP mmHg	SBP mmHg	BL DBP mmHg	DBP mmHg	BL PR	PR	TG (%)	TC (%)	HDL-C (%)	LDL-C (%)
Rosenstock SUPASS-1 40 weeks	None	TZP5 TZP10 TZP15 PBO	121 121 121 115	128	-4.7 -5.2 -4.7 -2.0	79	-2.9 -3.1 -3.4 -1.4	74	0.8 2.2 1.3 1.2	-28 -28 -32 7.0	-5.5 -6.3 -8.4 -0.8	2.1 1.4 3.2 -1.6	-6.7 -7.7 -12.6 -1.7
Frias SURPASS-2 40 weeks	MET	TZP5 TZP10 TZP15 SEM1	470 469 470 469	131	-4.8 -5.3 -6.5 -3.6	79	-1.9 -2.5 -2.9 -1.0	75	2.3 2.2 2.6 2.5	-19 -24* -25* -11	-5.5 -6.0 -6.3 -4.8	6.8 7.9 7.1 4.4	-7.7 -5.6 -5.2 -6.4
Ludvik SURPASS-3 52 weeks	MET (68%) MET+SGLT2i (32%)	TZP5 TZP10 TZP15 IDEG^	358 360 359 360	132	-4.9 -6.6 -5.5 0.5	79	-2.0 -2.5 -1.9 0.4	75	0.9 0.7 2.7 0.6	-20 -51 -46 -14	-3.7 -11.3 -10.4 -7.0	2.4* 5.2* 4.8* 1.1	-3.0 -5.8 -5.6 -4.4
SURPASS-4	1-3 OADs (MET, SGLT2i, SU)	TZP5 TZP10 TZP15 IGLA	329 328 338 1000	134	-2.8 -3.7 -4.8 +1.3	78	-1.0 -0.8 -1.0 +0.7	73	2.9 3.2 4.1 1.2	-16 -20 -22 -6	-5.1 -5.5 -5.6 0	6.7 9.7 10.8 2.9	-6.8 -8.3 -7.9 1.4
SURPASS-5 40 weeks	IGLA±MET (BL IGLA 34U)**	TZP5 TZP10 TZP15 PBO	116 119 120 120	138	-6.1 -8.3 -12.6 -1.7	81	-2.0 -3.3 -4.5 -2.1	75	1.3 3.5 5.6 -0.8	-15 -19 -25 -7	-9 -10 -13 -0.4	2.1 1.8 0.9 1.7	-9 -13 -16 3

Abbreviations: BL=baseline; DBP=diastolic blood pressure, HDL-C= high density lipoprotein-cholesterol; IDEG=insulin degludec; IGLA=insulin glargine; LDL-C=low density lipoprotein-cholesterol; MET=metformin; OAD=oral antidiabetic drugs; PBO=placebo; PR=pulse rate; SBP=systolic blood pressure; SEM=semaglutide; SGLT2i= sodium-glucose cotransporter-2 inhibitor; SU=sulfonylurea; TC=total cholesterol; TG=triglycerides; TZP=tirzepatide

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