EU Risk Management Plan (Version 2.1)

Global Patient Safety
Signatory information is available on request.
EU Risk Management Plan electronically approved by Lilly on date provided below.

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EU Risk Management Plan for Mounjaro (Tirzepatide)

RMP version to be assessed as part of the application: 2.1

Data lock point for this RMP: 10 June 2022

Date of final sign off: Refer to the cover page

Rationale for submitting an updated RMP:

To include the proposed new indication of chronic weight management.

Summary of significant changes in this RMP:

The summary of changes made in the applicable sections in the RMP are as follows:

- A proposed new indication of chronic weight management (CWM) is included along with relevant information on incidence, prevalence, demography, main existing treatment options, natural history of the indicated condition, and important comorbidities,
- Updated overall cumulative exposure in Tirzepatide clinical trial program and exposure in special populations.
- Updated information on important potential risks considering the proposed new indication of CWM.
- Minor editorial changes have been made.

Other RMP versions under evaluation

RMP version number: v1.1

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Details of the currently approved RMP

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's Qualified Person for Pharmacovigilance (QPPV). The electronic signature is available on file.

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List of Abbreviations

Term	Definition
ASCVD	atherosclerotic cardiovascular disease
Association	causal association
BMI	body mass index
CI	confidence interval
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
CV	cardiovascular
DR	diabetic retinopathy
EMA	European Medicines Agency
EPAR	European Public Assessment Report
GI	Gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HbA1c	glycosylated haemoglobin A1c
HR	hazard ratio
MACE	major adverse cardiac events
MTC	medullary thyroid cancer
PASS	post-authorisation safety study
QW	once weekly
RA	receptor agonist
SC	Subcutaneous
SGLT2	sodium-dependent glucose cotransporters-2
SmPC	summary of product characteristics
RMP	risk management plan
T2DM	type 2 diabetes mellitus

Part I: Product(s) Overview

Table Part I. 1. Product Overview

Active substance(s) (INN or common name)	Tirzepatide
Pharmacotherapeutic group(s) (ATC Code)	A10BX16
Marketing Authorisation Holder	Eli Lilly Nederland B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Mounjaro

Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** GIP and GLP-1 receptor agonist
	Summary of mode of action: As a long-acting incretin agonist, tirzepatide combines the signalling of each receptor resulting in glucose-dependent increase in insulin secretion, reduced glucagon secretion, reduced insulin resistance, and decreased food intake through the regulation of appetite. These actions enable improved glycaemic control and body weight loss.
	Important information about its composition: Tirzepatide is a GIP and GLP-1 receptor agonist. It is a 39-amino-acid synthetic peptide engineered from the native GIP sequence modified to bind to both the GIP and GLP-1 receptors and includes a C20 fatty di-acid moiety. It has a half-life of approximately 5 days that makes it suitable for once weekly administration.
Hyperlink to the Product Information	See eCTD Module 1.3.1
Indication(s) in the EEA	**Current:** Tirzepatide is indicated for the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise • as a monotherapy when metformin is considered inappropriate due to intolerance or contraindications, and in addition to other medicinal products for the treatment of diabetes.
	Proposed: Tirzepatide is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management, including weight loss and weight maintenance, in adults with an initial body mass index (BMI) of • ≥30 kg/m^2 (obesity) or • ≥27 kg/m^2 to <30kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus).
Dosage in the EEA	**Current:** The starting dose of tirzepatide is 2.5 mg once weekly. After 4 weeks, increase the dose to 5 mg once weekly. If needed, dose increases can be made in 2.5-mg increments after a minimum of 4 weeks on the current dose. The recommended doses are 5, 10, and 15 mg. The maximum dose is 15 mg once weekly.

Pharmaceutical form(s) and strengths	**Current:** The medicinal product is a solution for injection, provided in the following strengths: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15mg.
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ATC = Anatomical Therapeutic Chemical; eCTD = electronic common technical document; EEA = European Economic Area; EU = European Union; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; INN = International Non-proprietary Names; RMP = risk management plan; T2DM = type 2 diabetes mellitus.

Part II: Safety Specification

Module SI - Epidemiology of the Indication(s) and Target Population(s)

SI.1 Type 2 Diabetes Mellitus

SI.1.1 Incidence

Estimates of incidence rates for chronic diseases like T2DM are not well characterised, predominately due to the challenges in distinguishing new (incident) cases from existing (prevalent) cases in data sources. In general, the incidence rates of diabetes are 6.9 and 6.8 cases per 1000 people in the US and Canada, respectively (PHAC 2011; CDC 2020). Annually, 1.5 million Americans are diagnosed with diabetes, and T2DM accounts for 90% to 95% of all diabetes cases (ADA 2018; CDC 2020).

Between 2014 and 2015, 5758 children and adolescents (aged 10 to 19 years old) were newly diagnosed with T2DM in the US (CDC 2020). In the UK, the incidence of T2DM among patients aged 16 years and older in 2014 was about 369 per 100,000 person-years (Zghebi et al. 2017). In Sweden, the incidence of T2DM in 2013 was 399 per 100,000 people (Norhammar et al. 2016).

SI.1.2 Prevalence

Globally, the prevalence of T2DM is estimated to increase from 2.8% in 2000 to 4.4% in 2030 (Celik 2018), and 1 in 3 Americans is expected to have T2DM by 2050 (Bhupathiraju and Hu 2016). About 10% of the US population in 2018 and the Canadian population in 2011 had diabetes (PHAC 2011; CDC 2020).

In Europe, the prevalence of diabetes among adults aged 18 years and older was 9.1% in 2017 and is estimated to be 10.8% in 2045 (IDF 2017). In the UK, the prevalence of T2DM in individuals aged 16 years and older was 5.3% in 2014 (Zghebi et al. 2017). Approximately, 7% of German population had T2DM in 2010 (Tamayo et al. 2016).

SI.1.3 Demographics of the Population in the proposed Indication and Risk Factors for the Disease

In the US, over time, the prevalence of diabetes has increased significantly in all age groups, in both sexes, in all race groups, and in all education categories (Bhupathiraju and Hu 2016). The 2018 prevalence of diagnosed diabetes, with the majority being T2DM, increased with age as follows: age 18 to 44 years, 3%; age 45 to 64 years, 14%; and age 65 years and older, 21%, with men having higher prevalence rate than women (11% vs. 9.5%) (CDC 2020).

In Europe, no difference between men and women in diabetes prevalence was observed (approximately 19% each) (WHO[WWW]). However, the 2005 prevalence of diabetes among men and women in European regions was 13% and 9% in the Northwest, 15% and 12% in the South, and 11% and 10% in the East, respectively (Fox et al. 2009).

Globally, more than 200 million women (aged 20 to 79 years) had diabetes in 2017, which is projected to increase to more than 300 million by 2045, and 1 in 3 women with diabetes are of

reproductive age (IDF 2018). Between 2007 and 2010, 3.2% of women aged 20 to 44 years old had diabetes in the US (Kim et al. 2018). Of the annual deliveries in England and Wales, up to 5% of women have pre-existing diabetes or gestational diabetes (NICE 2015).

Among the risk factors for T2DM are overweight and obesity, physically inactive lifestyle, prediabetes, gestational diabetes, have a family history of T2DM, aged 45 years or older, and African American and Hispanic ethno-racial groups (CDC 2021).

SI.1.4 Main Existing Treatment Options

All patients with T2DM should receive standardised self-management education, important components of which include nutrition, exercise management, and weight loss, as appropriate (i.e., lifestyle changes).

As currently described in international guidelines, the management of hyperglycaemia for most patients with T2DM comprises stepwise increases in treatment when glycaemic control can no longer be maintained (Davies et al. 2018; ADA 2021). Metformin should be started with lifestyle modification at the time of T2DM diagnosis, unless there are contraindications. Although all the additional classes of therapies listed within this section are existing treatment options, the choice of additional therapy is individualised based on patient preference, therapeutic goals, and clinical characteristics, including but not limited to the presence or absence of CV disease, heart failure, or CKD. The following is a list of the more common agents used to treat T2DM:

<u>Oral antidiabetic agents</u>

- Biguanides (e.g., metformin) are widely used as a first-line therapy; can promote modest weight loss; have a low risk of hypoglycaemia; may have GI side effects; associated with a rare risk of lactic acidosis (Lalau 2010) and potential for B12 deficiency and a listed contraindication for use includes severe renal failure.
- Sulphonylureas (e.g., glimepiride, glyburide, glipizide) have a moderate-to-severe risk of hypoglycaemia and are associated with weight gain (Garber et al. 2019).
- Thiazolidinediones (e.g., pioglitazone and rosiglitazone) have a low risk of hypoglycaemia; are associated with weight gain and have an increased risk of oedema/heart failure.
- Dipeptidyl peptidase-4 inhibitors (e.g., sitagliptin, saxagliptin, algolipitn, and linagliptin) have a low risk of hypoglycaemia; are weight neutral, potential risk of pancreatitis has been described (although a causal relationship has not been established) and potential risk of heart failure with saxagliptin.
- Sodium-glucose cotransporter-2 inhibitors (e.g., canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) are associated with a low risk of hypoglycaemia and weight reduction (Garber et al. 2019); shown a benefit for atherosclerotic cardiovascular disease (ASCVD; empagliflozin), heart failure (empagliflozin, dapagliflozin), and progression of CKD (canagliflozin); are associated with an increased risk of urinary tract and genital infections, risk of volume depletion and hypotension; and are associated with a rare risk of ketoacidosis, and bone fractures (canagliflozin).

- Oral GLP-1 RA semaglutide has a low risk of hypoglycaemia; is associated with weight reduction; has GI side effects; has been associated with a potential increased risk of pancreatitis (although a causal relationship has not been established); and based on evidence from studies in rodents, a potential risk of MTC cannot be excluded.

Injectable therapies

- Glucagon-like peptide-1 RAs (e.g., dulaglutide, exenatide, exenatide once weekly, liraglutide, lixisenatide, and semaglutide) are administered via SC injection; have a low risk of hypoglycaemia; are associated with weight reduction; shown benefit for ASCVD (dulaglutide, liraglutide, and semaglutide); have GI side effects; have been associated with a potential increased risk of pancreatitis (although a causal relationship has not been established); and based on evidence from studies in rodents, a potential risk of MTC cannot be excluded.
- Insulin (human insulin and insulin analogues) is administered via SC injection; is universally effective; has a moderate-to-high risk of hypoglycaemia; and can be associated with weight gain (Garber et al. 2019).

The consensus report by the American Diabetes Association and European Association for the Study of Diabetes recommends metformin as the preferred initial glucose-lowering medication for most patients with T2DM. Patients with T2DM and with established CV disease can be considered for treatment with GLP-1 RAs or SGLT2 inhibitors to reduce MACE, hospitalisation for heart failure, CV death, or CKD progression independent of baseline HbA1c or individualised HbA1c target. The updated report also suggests that GLP-1 RA can also be considered in patients without established CV disease but with the presence of specific indicators of high CV risk to reduce MACE. In addition, SGLT2 inhibitors can be considered in patients with T2DM and heart failure, particularly those with heart failure with reduced ejection fraction to reduce hospitalisation for heart failure, MACE, and CV death.

SI.1.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

Morbidity: Patients with T2DM have a risk for significant morbidity if left untreated, including microvascular and macrovascular complications. Cardiovascular disease is the leading cause of T2DM complications (32% prevalence rate and 68% mortality rate) (Bhupathiraju and Hu 2016; Einarson et al. 2018).

In Sweden, about 34% of adults with T2DM had CV disease in 2013 (Norhammar et al. 2016). In Europe, 35% of patients with coronary heart disease have diabetes (Gyberg et al. 2015). Patients with diabetes are about 3-times more likely to have a stroke than those without diabetes (Air and Kissela 2007). Type 2 diabetes mellitus is associated with numerous negative health effects, including increased mortality and risks of comorbidities that are described in Section SI.1.6.

Mortality: Individuals with T2DM are more likely to die prematurely than those without T2DM. Diabetes accounts for 10% of deaths in Canada (CDA 2019). In 2016, diabetes was the seventh leading cause of death in the US (accounting for 2.9% of all deaths in 2016), with corresponding

mortality rate of 24.8 deaths per 100,000 people (27.5 in men and 22.1 in women) (Heron 2018). In Europe, almost 700,000 deaths were attributed to T2DM in 2017 among adults aged ≥20 years (IDF 2017).

In Germany, 16% of all deaths in 2010 were attributed to T2DM (Jacobs et al. 2017), with age- and gender-standardised all-cause mortality rate about twice as high for adults with T2DM as for the general population (18.3 vs. 10.1 deaths per 1000 person-years) (Röckl et al. 2017).

SI.1.6 Important Co-morbidities

The important comorbidities that may occur among patients with T2DM are listed in Table SI.1.

Table SI.1. Important Comorbidities Associated with T2DM

Comorbidity	Country	Prevalence, %
Cardiovascular disease	Worldwide (Einarson et al. 2018)	32
Atherosclerosis		29
Coronary artery disease		21
Heart failure		15
Angina pectoris		15
Myocardial infarction		10
Stroke		8
Cardiovascular disease	United States (CDC 2020)	7.5
Stroke		1
Ischaemic heart disease		2
Cardiovascular disease	Sweden (Rawshani et al. 2017)	
Myocardial infarction		9.1
Stroke		6.6
Coronary heart disease		17.3
Heart failure		6.7
Hypertension	Sweden (Colosia et al. 2013)	95
	Germany (Colosia et al. 2013)	93
	United Kingdom (Colosia et al. 2013)	86
	Belgium (Colosia et al. 2013)	80
	United States (Colosia et al. 2013)	71
	Turkey (Eren et al. 2014)	95
Hyperlipidaemia	United States (Chehade et al. 2013)	25
	South Africa (Daya et al. 2017)	94
Obesity (based on BMI or waist circumference)	United Kingdom (Colosia et al. 2013)	64 or 97
	Germany (Colosia et al. 2013)	50 or 92
	Turkey (Eren et al. 2014)	52
Nephropathy	Sweden (Rawshani et al. 2017)	8.5
	United States (Shahinian et al. 2013)	25
	Turkey (Eren et al. 2014)	23
	Japan (Fujishiro et al. 2017)	48
Retinopathy	Spain (Rodriguez-Poncelas et al. 2015)	12
	United States (Zhang et al. 2010)	29
	Turkey (Eren et al. 2014)	27
	Australia (Man et al. 2015)	53
	Japan (Fujishiro et al. 2017)	23

Comorbidity	Country	Prevalence, %
Neuropathy	Italy (Salvotelli et al. 2015) United States (Jaiswal et al. 2013) Japan (Fujishiro et al. 2017)	31 26 24
Malignancy	Sweden (Norhammar et al. 2016) United States (Li et al. 2013)	19 22

Abbreviations: BMI = body mass index; CDC = Center for Disease Control and Prevention; T2DM = type 2 diabetes mellitus.

SI.2 Chronic Weight Management

SI.2.1 Incidence

According to a US study of community-dwelling adults, 7% and 16% of individuals had developed obesity at the 1- and 3-year follow-up, respectively (DeJesus et al. 2022).

In a UK study of children and adolescents aged 7 to 15 years, the 4-year cumulative incidence of obesity was higher in children aged 7 to 11 years than 11 to 15 years, 5.0% and 1.4%, respectively (Hughes et al. 2011). Similarly, in a Spanish study of children and adolescents aged 2 to 17 years, children aged 6 to 7 years had the highest incidence rate of obesity among boys and girls, 4.9 and 3.9 per 100 person-years, respectively (de Bont et al. 2020).

SI.2.2 Prevalence

Data from the US NHANES report that the prevalence of obesity in adults has tripled over the past 60 years, with the age-adjusted prevalence increasing from 13.4% in 1960 to 1962, to 42.4% in 2017 to 2018 (Fryar et al. 2020; Hales et al. 2020).

In 2016, the worldwide prevalence of obesity in adults aged at least 18 years was 13%, ranging from 4% to 42.4% in various countries. The prevalence of obesity among adults in various countries is listed here (IPD 2022).

Country	Prevalence Rate (%) (IPD 2022)
US	42.4
Canada	31.0
Australia	30.0
UK	27.7
Spain	27.0
Germany	23.6
Italy	23.0
Brazil	20.3
France	17.0
China	5.2
Japan	4.0

Nationally representative data in the US demonstrate that childhood obesity is a significant concern and continues to increase over time (Skinner et al. 2018). The prevalence of obesity among children aged 2 to 19 years has nearly quadrupled over the past 50 years, increasing from

5.2% in 1971 to 1974, to 19.3% in 2017 to 2018, as per data from the NHANES (Fryar et al. 2020).

Worldwide, the prevalence of childhood obesity is on the rise (Skinner et al. 2018; Weihrauch-Bluher and Wiegand 2018). Age-standardised global prevalence is reported to have increased from 0.7% and 0.9% for girls and boys, respectively, in 1975 to 5.6% and 7.8% for girls and boys, respectively, in 2016 (Klingelhofer et al. 2021). The literature reports an increase in obesity in children under 5 years of age in Vietnam from 1.4% in 1998 to 4.6% in 2010 (Do et al. 2017). In a review of global increases in childhood obesity from 1980 to 2015, the highest increase was reported among children in Saudi Arabia (9.33% and 8.52% increase among girls and boys, respectively), followed by the US (7.29% and 7.99% increase among girls and boys, respectively) (Klingelhofer et al. 2021). Girls in Egypt, Brazil, and Mexico experienced an increase in obesity of 6.76%, 5.70%, and 5.56%, respectively. For boys in Brazil and Canada, the increase in obesity prevalence was reported as 7.69% and 6.73%, respectively (Klingelhofer et al. 2021).

SI.2.3 Demographics of the Population in the Indication – Age, Gender, Racial and/or Ethnic origin (When Relevant for Assessment of Safety and Risk Management) and Risk Factors for the Disease

Gender

Overall, the prevalence of obesity is higher in women than men, globally, and this trend is consistent across the World Bank regions and World Bank income groups, including low-, middle-, and high-income countries (Kanter and Caballero 2012; Cooper et al. 2021). In 2016, the global prevalence of obesity was 15% in women and 11% in men (WHO 2021). The results from a US survey reported the age-adjusted prevalence of obesity in 2013 to 2014 was higher in women (40.4%) than men (35.0%) (Flegal et al. 2016). Although more recent NHANES data from 2017 to 2018 did not detect a gender gap in overall obesity prevalence, severe (Class 3) obesity was reported to be higher in women than men (11.5% versus 6.9%, respectively) (Hales et al. 2020). At a country level, there are some exceptions; for example, in Japan, the prevalence of overweight and obesity were 40.3% and 11.2% in men, and 18.6% and 7.1% in women, respectively (Hasegawa et al. 2020).

Age

Obesity is increasingly prevalent among both the adult and paediatric populations. In 2017 to 2018, the US prevalence was

- 40.0% among younger adults aged 20 to 39 years
- 44.8% among middle-aged adults aged 40 to 59 years, and
- 42.8% among older adults aged 60 year and above.

The differences were not significant. Class 3 obesity, however, was significantly different by age group with the highest prevalence among adults aged 40 to 59 years (11.5%), followed by adults aged 20 to 39 years (9.1%), and adults aged 60 years and above (5.8%) (Hales et al. 2020). The

US prevalence of paediatric obesity in 2017 to 2020 increased with increasing age. The prevalence was 12.7%, 20.7%, and 22.2% in those aged 2 to 5 years, 6 to 11 years, and 12 to 19 years, respectively (CDC 2022). A sharp increase in obesity has been observed among children aged 2 to 5 years, most notable in males whose prevalence increased 40% from 2011 to 2016 (Skinner et al. 2018).

Ethnicity

There are notable disparities in obesity prevalence across ethnic/racial subgroups in the US. These disparities appear to be driven by differential sociocultural influences, socioeconomic status, health behaviours, neighbourhood environments, and early childhood health factors (Min et al. 2021). The highest age-adjusted prevalence of obesity in the US was seen in non-Hispanic Blacks (49.9%), followed by Hispanics (45.6%), and non-Hispanic Whites (41.4%) (NCHS 2021). Similar to adults, the prevalence of obesity in children was highest in Hispanic (26.2%) and non-Hispanic Black children (24.8%) (CDC 2022).

Risk factors

Per NIH 2022, there are many risk factors for obesity including

- lifestyle factors, such as
    - high calorie-low nutrient foods
    - inadequate or poor-quality sleep
    - no or low physical activity
    - stress
    - circadian disruption
- environmental factors, for example, chemical endocrine disruptors
- a host of weight gain-promoting medications
- family history and genetics, and
- developmental factors, that is, epigenetics.

In a study of community-dwelling adults, those who were overweight at baseline had a significantly higher risk of developing obesity at the 1- and 3-year follow-ups when compared with those who were normal weight. The unadjusted HR was 13.4 (95% CI: 11.48 to 15.49) and 11.9 (95% CI: 10.87 to 13.14), respectively (DeJesus et al. 2022).

Childhood obesity is also a significant risk factor for adult obesity (WHO 2021). A systematic review and meta-analysis reported that approximately 55% of children with obesity go on to have obesity in adolescence. About 80% of adolescents with obesity will still have obesity in adulthood and about 70% will have obesity over age 30 years (Simmonds et al. 2016).

SI.2.4 Main Existing Treatment Options

Obesity is a treatable disease. Obesity treatment strategies may include nutritional and behavioural interventions, pharmacological agents, and/or bariatric (metabolic) surgery.

For those with established co-morbidities, achieving greater than 10% body weight reduction can substantially improve and successfully reverse the course of some conditions. These conditions

may include T2DM, obstructive sleep apnoea, gastroesophageal reflux, CV disease outcomes, and CV disease risks, such as dyslipidaemia, and hypertension (Gregg et al. 2016; Haase et al. 2021; Sarma et al. 2021; Sutanto et al. 2021).

Behavioural and nutritional interventions

Lifestyle approaches, based on caloric restriction, physical activity, and behavioural therapy, yield an average 5% to 10% body weight reduction. This degree of weight reduction has been associated with some improvement in obesity-related CV risk factors, and in some cases, improved health-related quality of life (Mertens and Van Gaal 2000; Knowler et al. 2002; Jensen et al. 2014; Kolotkin and Andersen 2017). However, lifestyle therapies alone fail to achieve sustainable weight reduction in most individuals with obesity.

Caloric restriction through lifestyle change, for example, has been shown to lead to metabolic adaptive responses, including increases in hunger hormones, decreases in satiety factors (including gastrointestinal peptides), increased appetitive drive and food intake, and lower energy expenditure (Leibel et al. 1995; Sumithran et al. 2011). These adaptations are thought to work in concert to cause regain and poor durability of treatment such that only 20% of individuals can maintain a 10% weight reduction at 1 year with lifestyle-based treatment (Wing and Hill 2001).

Moreover, weight reduction beyond that achieved with lifestyle alone, for example, more than 10% weight reduction, is often needed for the resolution of obesity-related co-morbidities and reduction of CV mortality (Wing et al. 2011).

Bariatric surgery for managing obesity

Bariatric (or metabolic) surgery remains an effective option for select people with obesity:

- BMI at least 30 kg/m^2 with uncontrolled T2DM
- BMI 35 to 39.9 kg/m^2 with co-morbidities, and
- BMI at least 40 kg/m^2 irrespective of co-morbidities.

Individuals who undergo bariatric surgery lose an average of 25% to 30% body weight. Data indicate that patients who undergo bariatric surgery have improvements in T2DM, reduced CV risk, improvements in health-related quality of life, and decreased risk of death due to CV events and cancer (Schauer et al. 2012, 2017; Sjöström et al. 2012). During the COVID-19 pandemic, individuals who underwent bariatric surgery were at a lower risk for hospitalisation, need for supplemental oxygen, and severe COVID-19 infection than those with obesity who did not (Aminian et al. 2022).

Although bariatric surgery is available for select individuals with obesity, and laparoscopic approaches and multidisciplinary care have substantially reduced complication rates over time, surgical procedures are still associated with some risk of peri-operative and post-operative complications (Opperer et al. 2016; Currie et al. 2021). Due to a combination of lack of awareness, limited access, and apprehension regarding the invasive and permanent nature of bariatric surgery, less than 1% of the eligible population receives bariatric surgery as a treatment

for obesity (ASMBS 2021), resulting in a significant unmet medical need for this patient population.

Current pharmacological agents for treating obesity

Because there is limited efficacy of lifestyle intervention alone, and substantial efficacy but poor scalability of surgical approaches, there is a considerable treatment gap in obesity care that pharmacologic innovation has sought to address over the past 30 years. Despite numerous efforts, there remains an unmet need in the pharmacologic treatment of obesity for drugs that are safe, substantially efficacious, and well tolerated. Current guidance recommends the use of approved anti-obesity medications in individuals with BMI at least 30 kg/m^2, or at least 27 kg/m^2 with 1 or more weight-related comorbid condition (Apovian et al. 2015). Until recently, anti-obesity medications used in conjunction with behaviour modifications demonstrated single digit average percentage body weight reductions with only a small fraction of individuals maintaining greater than 10% weight reduction at tolerable doses.

The GLP-1 RA class has entered the paradigm as a treatment option for patients with obesity. Studies with these agents have demonstrated greater body weight reductions compared with other anti-obesity medications, with some GLP-1 RAs achieving a 12.4% change in baseline body weight compared with placebo (Wilding et al. 2021). Additionally, GLP-1 RA effects may provide beneficial CV risk reduction and improvement in inflammation that make this a promising therapeutic class in patients with T2DM, obesity, or both conditions (Ryan et al. 2020; Wilding et al. 2021).

SI.2.5 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Obesity is a chronic, progressive, and relapsing disease associated with substantial morbidity and mortality.

Morbidity

Complications of obesity vary and may develop and progress over time. For example, most individuals who may be clinically assessed as having “metabolically healthy obesity” eventually develop metabolic abnormalities and clinical disease like hypertension and T2DM (Echouffo-Tcheugui et al. 2019). Obesity-related complications span cardiometabolic, inflammatory, degenerative, mechanophysical, neoplastic, and psychological conditions (Wilding and Jacob 2021). Obesity significantly impacts patients’ daily activities and quality of life (Poon et al. 2022).

Most individuals with obesity engage in multiple attempts in weight reduction throughout the course of their disease. Data from 2013 to 2016 NHANES indicated that 49.1% of US adults tried to lose weight just within the past 12 months (Martin et al. 2018). As lifestyle-based strategies infrequently lead to durable weight reduction, many people regain weight after each attempt leading to weight cycling. Although the effects of weight cycling on health outcomes are a source of debate, repeated dieting and weight cycling have been implicated in an increased risk

for eating disorders, other psychological disorders, and multiple co-morbidities including T2DM, hypertension, cancer, bone fractures, and increased mortality (Rhee 2017).

Mortality

Obesity has been associated with significantly higher all-cause mortality when compared with normal weight (BMI of 18.5 to less than 25 kg/m^2), HR 1.18 (95% CI: 1.12 to 1.25) (Flegal et al. 2013). In 2015, excess body weight accounted for approximately 4 million deaths and 120 million disability-adjusted life-years worldwide (The GBD 2015 Obesity Collaborators 2017). Secondary to the emergence of multisystem comorbid disease, obesity shortens life expectancy by 3 years, with Class 3 obesity decreasing life expectancy by up to 20 years (OECD 2019; Müller et al. 2021).

Childhood obesity

Childhood obesity is associated with a higher chance of obesity, premature death, and disability in adulthood. In addition to these increased future risks, children with obesity experience breathing difficulties, increased risk of fractures, hypertension, early markers of CV disease, insulin resistance, and psychological effects (WHO 2021).

SI.2.6 Important Co-morbidities

Obesity has been associated with increased risk of multiple conditions (Müller et al. 2021), including

- atherosclerotic CV disease, including coronary artery disease, myocardial infarction, and stroke
- heart failure
- arrhythmias, including atrial fibrillation
- T2DM
- non-alcoholic steatohepatitis
- depression
- obstructive sleep apnoea
- osteoarthritis, and
- 13 types of cancers.

Recently, studies indicated that individuals with obesity were more likely to be hospitalised, require mechanical ventilation, and die from COVID-19 than those without obesity (Foo et al. 2021; Gao et al. 2021; Smati et al. 2021).

Module SII – Nonclinical Part of the Safety Specification

SII.1 Toxicity

Thyroid safety

- Consistent with the long-acting medicinal products in the GLP-1 RA class, an increased incidence of thyroid C-cell adenomas and carcinomas occurred in all tirzepatide-treated groups in a rat carcinogenicity study. No changes in thyroid C-cells were observed in monkey studies with tirzepatide which is also consistent with the lack of effect in monkeys for other GLP-1 RAs (Bjerre Knudsen et al. 2010; Vahle et al. 2015). The relevance of rodent thyroid tumours to humans is not known.

Reproductive and developmental safety

- In a female fertility study in rats, oestrous cycles were disrupted and numbers of corpora lutea were decreased in all tirzepatide-treated groups. These effects were considered secondary to the decreased body weight and food consumption noted at all dose levels. Although corpora lutea formation was decreased, there were no effects on mating, fertility, conception, or embryonic survival in any treated group.

- In pregnant rats and rabbits that were given tirzepatide, developmental effects occurred only in conjunction with maternal toxicity and included
  - reduced foetal weights in both species, and
  - increased numbers of malformations and developmental variations in rats.

- In a male fertility study in rats, there were no effects on mating, fertility, sperm analysis, or reproduction.

SII.2 Safety Pharmacology

Cardiovascular safety

In the single-dose safety pharmacology study in monkeys, tirzepatide effects were consistent with incretin pharmacology and consisted of

- increased heart rate
- increased diastolic blood pressure
- increased mean arterial pressure, and
- decreased dP/dt_{max} (rate derivative for change in ventricular pressure over time; index of cardiac contractility).

Given the observed effect on heart rate and blood pressure, changes in dP/dt_{max} would be expected. There were no effects on corrected QT interval.

SII.3 Other Toxicity-Related Information or Data

Tirzepatide-related changes in both rat and monkey repeat-dose toxicity studies up to 6 months in duration, were generally consistent with, or secondary to, incretin pharmacology. The primary effects of tirzepatide administration to rats were dose-dependent decrease in food consumption

and decrease in body weight gain or body weight loss or both. None of these effects were considered adverse to the health of the animals and no dose-limiting target organ toxicity was observed.

Module SIII - Clinical Trial Exposure

This section contains the cumulative patient exposure from all completed Phase 2 and 3 clinical trials across all indications.

Table SIII.1. Duration of Exposure

Duration of Exposure[a]	Patients (Number of patients)	Person Time (Patient-Year)[b]
Type 2 Diabetes Mellitus		
Phase 2 and 3 Studies		
>0 to <4 weeks	101	3.6
≥4 to <8 weeks	132	14.5
≥8 to <12 weeks	119	21.7
≥12 to <16 weeks	176	43.5
≥16 to <20 weeks	86	28.3
≥20 to <24 weeks	57	23.1
≥24 to <36 weeks	328	176.8
≥36 to <48 weeks	2512	1933.2
≥48 to <52 weeks	216	211.5
≥52 to <72 weeks	1697	1751.6
≥72 to <104 weeks	661	1073.8
≥104 weeks	17	34.0
Total	6102	5315.6
Chronic Weight Management		
Phase 3 Studies		
>0 to <4 weeks	27	0.8
≥4 to <8 weeks	41	4.1
≥8 to <12 weeks	32	5.6
≥12 to <16 weeks	36	9.0
≥16 to <20 weeks	37	12.2
≥20 to <24 weeks	23	9.4
≥24 to <36 weeks	124	75.3
≥36 to <48 weeks	667	467.4
≥48 to <52 weeks	19	17.8
≥52 to <72 weeks	227	296.9
≥72 to <104 weeks	1445	2005.4
Total	2678	2903.9

[a] Duration of study treatment is defined as time in days from date of first dose of study treatment to date of last dose of study treatment plus 7 days.

[b] Patient-year is calculated as sum of duration of exposure in days for all patients at specified interval/365.25.

The table below provides exposure in participants with BMI at least 27 kg/m^2 from all Phase 2 and 3 T2DM clinical trials and all participants from Phase 3 CWM clinical trials.

Table SIII.2. Duration of Tirzepatide Exposure in Participants with BMI ≥27 kg/m2 at Baseline

Duration of Exposure[a]	Patients (Number of patients)	Person Time (Patient-Year)[b]
Phase 2 and 3 Studies		
>0 to <4 weeks	100	3.3
≥4 to <8 weeks	119	12.6
≥8 to <12 weeks	97	17.4
≥12 to <16 weeks	157	38.8
≥16 to <20 weeks	91	29.7
≥20 to <24 weeks	58	23.5
≥24 to <36 weeks	394	220.8
≥36 to <48 weeks	2666	2006.0
≥48 to <52 weeks	180	175.4
≥52 to <72 weeks	1465	1586.3
≥72 to <104 weeks	2014	2931.4
≥104 weeks	13	26.1
Total	7354	7071.3

Abbreviation: BMI = body mass index.

[a] Duration of exposure is defined as time in days from date of first dose of study treatment to date of last dose of study treatment plus 7 days.

[b] Patient-year is calculated as sum of duration of exposure in days for all participants at specified interval/365.25.

Table SIII.3. Age Group and Gender

Age group	Patients (number of patients)		Person time (Patient-year)[a]	
Type 2 Diabetes Mellitus				
Phase 2 and 3 Studies	**M**	**F**	**M**	**F**
≥ 18 to <65 years	2521	1859	2203.7	1551.4
≥ 65 to <75 year	857	643	788.6	570.3
≥ 75 to <85 years	123	92	119.9	74.8
≥ 85 years	2	5	1.5	5.4
Total	3503	2599	3113.8	2201.8
Chronic Weight Management				
Phase 3 Studies				
≥18 to <65 years	789	1689	862.0	1846.4
≥65 to <75 year	58	127	53.3	130.3
≥75 to <85 years	7	8	5.7	6.3
Total	854	1824	921.0	1983.0

Abbreviations: F = female; M = male.

[a] Patient-year is calculated as sum of duration of exposure in days for all patients in each age/gender group/365.25.

Table SIII.4. Age Group and Gender in Participants with BMI ≥27 kg/m² at Baseline

Age Group	Patients (Number of Patients)		Person Time (Patient-Year)[a]	
Phase 2 and 3 Studies	**M**	**F**	**M**	**F**
≥18 to <65 years	2677	3232	2552.1	3159.9
≥65 to <75 year	654	627	619.8	583.4
≥75 to <85 years	80	80	84.3	66.3
≥85 years	1	3	0.8	4.8
Total	3412	3942	3256.9	3814.4

Abbreviations: BMI = body mass index; F = female; M = male.

[a] Patient-year is calculated as sum of duration of exposure in days for all patients in each age or gender group/365.25.

Table SIII.5. Dose

Dose of exposure	Patients (Number of Patients)	Person Time (Patient-Year)[a]
Type 2 Diabetes Mellitus		
Phase 3 Studies[b]		
Tirzepatide 5 mg	1701	1587.7
Tirzepatide 10 mg	1702	1569.0
Tirzepatide 15 mg	1716	1564.3
Phase 3 Study (I8F-MC-GPHO)		
Tirzepatide 5 mg	230	168.6
Tirzepatide 10 mg	228	155.8
Tirzepatide 15 mg	229	158.1
Phase 2 Study (I8F-MC-GPGB)		
Tirzepatide 1 mg	52	23.2
Tirzepatide 5 mg	55	25.0
Tirzepatide 10 mg	51	23.2
Tirzepatide 15 mg	53	18.7
Phase 2 Study (I8F-MC-GPGF)		
Tirzepatide 12 mg	29	5.8
Tirzepatide 15 mg	56	11.2
Total	**6102**	**5310.6**
Chronic Weight Management		
Phase 3 Study (I8F-MC-GPHK)		
Tirzepatide 5 mg	630	806.5
Tirzepatide 10 mg	636	797.2
Tirzepatide 15 mg	630	797.9
Phase 3 Study (I8F-MC-GPHN)[c]		
Tirzepatide MTD (10 or 15 mg)	782	502.4
Total	**2678**	**2904.0**

Abbreviation: MTD = maximum tolerated dose.

[a] Patient-year is calculated as sum of duration of exposure in days for all patients in each dosing regimen/365.25.

[b] Excludes Study GPHO.

[c] Data from the 36-week open-label tirzepatide lead-in period.

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Table SIII.6. Dose in Patients with BMI ≥27 kg/m2 at Baseline

Dose of Exposure	Patients (Number of Patients)	Person Time (Patient-Year)[a]
Phase 2 and 3 Studies		
Tirzepatide 1 mg[b]	42	19.3
Tirzepatide 5 mg	2159	2196.4
Tirzepatide 10 mg	2141	2164.4
Tirzepatide 12 mg[c]	23	4.9
Tirzepatide 15 mg	2207	2183.8
Tirzepatide MTD[d]	782	502.4
Tirzepatide All[d,e]	**7354**	**7071.2**

Abbreviations: BMI = body mass index; MTD = maximum tolerated dose.

[a] Patient-year is calculated as sum of duration of exposure in days for all patients in each dosing regimen/365.25.

[b] Patients in Phase 2 Study I8F-MC-GPGB received tirzepatide 1 mg.

[c] Patients in Phase 2 Study I8F-MC-GPGF received tirzepatide 12 mg.

[d] Patients in Phase 3 Study I8F-MC-GPHN received MTD (tirzepatide 10 or 15 mg).

[e] Data from the 36-week open-label tirzepatide lead-in period.

Table SIII.7. Ethnic Origin

Ethnic Origin	Patients (Number of Patients)	Person Time (Patient-Year)[a]
Type 2 Diabetes Mellitus		
Phase 2 and 3 Studies		
Hispanic	2082	1845.3
Non-Hispanic	2254	2026.9
Not reported	1766	1443.5
Total	6102	5315.6
Chronic Weight Management		
Phase 3 Studies		
Hispanic	1247	1373.2
Non-Hispanic	1280	1335.3
Not reported	151	195.5
Total	2678	2903.9

[a] Patient-year is calculated as sum of duration of exposure in days for all patients in each ethnic origin/365.25.

Table SIII.8. Ethnic Origin in Participants with BMI ≥27 kg/m2 at Baseline

Ethnic Origin	Patients (Number of Patients)	Person Time (Patient-Year)[a]
Phase 2 and 3 Studies		
Hispanic	3038	2984.4
Non-Hispanic	3251	3120.1
Not reported	1065	966.8
Total	7354	7071.3

Abbreviation: BMI = body mass index.

[a]Patient-year is calculated as sum of duration of exposure in days for all patients in each ethnic origin/365.25.

Table SIII.9. Racial Origin

Race	Patients (Number of Patients)	Person Time (Patient-Year)[a]
Type 2 Diabetes Mellitus		
Phase 2 and 3 Studies		
American Indian or Alaska native	359	319.6
Asian	1915	1583.9
Black or African American	199	150.8
Native Hawaiian or other Pacific islander	13	10.7
White	3575	3209.4
Multiple	38	38.9
Missing	3	2.3
Total	6102	5315.6
Chronic Weight Management		
American Indian or Alaska native	173	230.2
Asian	262	296.6
Black or African American	233	230.7
Native Hawaiian or other Pacific islander	9	9.9
White	1970	2100.3
Multiple	31	36.2
Total	2678	2903.9

[a] Patient-year is calculated as sum of duration of exposure in days for all patient in each race/365.25.

Table SIII.10. Racial Origin in Participants with BMI ≥27 kg/m2 at Baseline

Race	Patients (Number of Patients)	Person Time (Patient-Year)[a]
Phase 2 and 3 Studies		
American Indian or Alaska native	457	487.8
Asian	1255	1149.9
Black or African American	403	362.2
Native Hawaiian or Other Pacific Islander	18	16.0
White	5159	4988.3
Multiple	61	65.7
Missing	1	1.5
Total	7354	7071.3

Abbreviation: BMI = body mass index.

[a] Patient-year is calculated as sum of duration of exposure in days for all patients in each race/365.25.

Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

The important exclusion criteria in the pivotal clinical studies are summarised in the table below.

Criterion	Missing Information (Yes or No)	Reason and Rationale for Exclusion
Patients <18 years of age	No	• The safety and efficacy of tirzepatide in children aged less than 18 years has not yet been established. • Paediatric clinical trials for T2DM are under development. • The prevalence of T2DM in the paediatric population is low and currently liraglutide is the only GLP-1 RA approved for paediatric patients aged 10 to 17 years old. • Paediatric clinical trials are under development for obesity.Currently, liraglutide is the only GLP-1 RA approved for paediatric participants aged 12 to 17 years with obesity.
Women who are pregnant or breastfeeding	No	• No adequate and well-controlled studies of tirzepatide have been conducted in pregnant or nursing women. Therefore, there is a limited amount of data from the use of tirzepatide in pregnant women and women who are breastfeeding. • Insufficient data on the effects of tirzepatide on maternal health and foetus prohibited the inclusion of pregnant women in the Phase 2 and Phase 3 registration trials. • Studies in animals have shown reproductive toxicity. In pregnant rats and rabbits that were given tirzepatide, developmental effects, like reduced foetal weights, were observed in both species. Increased numbers of malformations and developmental variations in rats occurred only in conjunction with maternal toxicity.
Patients with renal impairment	No	• Severe CKD with associated comorbidities or concomitant medications might represent an important confounder in clinical trials. • The molecular weight of tirzepatide is 4.8 kDa, which while greater than that of non-biologic drugs, is still notably lower than the glomerular filtration cutoff of 30 to 50 kDa; hence, the impact of renal impairment on tirzepatide PK cannot be disregarded. However, tirzepatide is presumed to be degraded into component amino acids by protein catabolism pathways. • Many trials used metformin as a comparator or as background therapy. Metformin is contraindicated for patients with a higher severity of renal disease. • The available PK data (I8F-MC-GPGG) confirm that there is no accumulation of tirzepatide in patients with renal impairment. For this reason, no dosage adjustment is required in these patients. Additionally, in the Phase 3 T2DM and CWM programmes, there are limited amount of data from the use of tirzepatide in severe CKD (eGFR <30mL/min/1.73m^2 by CKD-EPI).

Criterion	Missing Information (Yes or No)	Reason and Rationale for Exclusion
Patients with hepatic impairment	No	• Severe hepatic disease with associated comorbidities/concomitant medications might represent an important confounder in clinical trials. However, NAFLD/NASH is a common co-morbidity in participants with obesity or T2DM, and participants with NAFLD/NASH were not excluded from the clinical development programmes. • Tirzepatide is presumed to be degraded into component amino acids by protein catabolism pathways. It is a synthetic peptide, and, hence, not expected to be bio-transformed by drug-metabolising enzymes. • The available PK data (I8F-MC-GPGQ) confirm that there are no clinically relevant effects of hepatic impairment on PK of tirzepatide. For this reason, no dosage adjustment is required in these patients.

Abbreviations: CKD = chronic kidney disease; CKD-EPI = chronic kidney disease epidemiology collaboration; CWM = chronic weight management; eGFR = estimated glomerular filtration rate; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis; PK = pharmacokinetics; GLP-1 RA = glucagon-like peptide-1 receptor agonist; T2DM = type 2 diabetes mellitus.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure. However, an estimated cumulative exposure of 18,143 participants in the tirzepatide clinical trial program and approximately 15,000 participants in the planned studies with an exposure duration of 3 to 5 years increases the ability to detect rare and cumulative effects of the drug.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table SIV.1. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Paediatric Patients	Studies in paediatric populations were not included in the initial clinical development programme. A Phase 3 study in paediatric patients with T2DM is planned to assess safety, efficacy, and PK/PD in children and adolescents aged 10 to <18 years old. One PK study and two Phase 3 studies (age groups: 6 to 11 and 12 to 17 years) in paediatric participants with obesity and/or overweight are planned for the indication of CWM

Type of Special Population	Exposure
Pregnant women	Pregnant and breastfeeding women were excluded at screening in the clinical trials due to the considerations described in Section SIV.1. During the tirzepatide clinical trial programme for T2DM and CWM, (regardless of BMI at study entry), 25 pregnancies (0.56%) were reported in tirzepatide-treated female participants. Additionally, 4 pregnancies were reported in the partner of male study participants. During the tirzepatide clinical trial programme, no cases of breastfeeding were reported.
Breastfeeding women	
Patients with relevant comorbidities	
Patients with hepatic impairment	In a completed clinical pharmacology study, I8F-MC-GPGQ, evaluating the PK and tolerability of a single 5-mg dose of tirzepatide, a total of 32 subjects were enrolled. Of these, 19 subjects were with mild, moderate, or severe hepatic impairment: • 6 subjects with mild hepatic impairment • 6 subjects with moderate hepatic impairment, and • 7 subjects with severe hepatic impairment.
Patients with renal impairment	In a completed clinical pharmacology study, I8F-MC-GPGG, evaluating the PK and tolerability of a single 5-mg dose of tirzepatide, a total of 45 subjects were enrolled. Of these, 31 subjects were with mild, moderate, severe renal impairment, or end-stage renal disease. Out of 7702 patients enrolled in the Phase 3 programme of T2DM and CWM (regardless of BMI at study entry), the number of tirzepatide-treated patients with renal impairment is as follows: • 16 with severe renal impairment (eGFR <30 mL/minute/1.73m^2) • 476 with moderate renal impairment (eGFR >30 to <60 mL/minute/1.73m^2), and • 2282 with mild renal impairment (eGFR >60 to <90 mL/minute/1.73m^2).

Type of Special Population	Exposure
Patients with CV impairment	In a completed Phase 3 study, I8F-MC-GPGM, evaluating the safety and efficacy of tirzepatide 5 mg, 10 mg and/or 15 mg in patients with T2DM and increased CV risk (coronary heart disease, peripheral arterial disease, cerebrovascular disease, CKD if >50 years old, congestive heart failure if >50 years old), a total of 2002 patients were enrolled. A Phase 3 study (I8F-MC-GPGN) is ongoing to assess the efficacy of maximally tolerated tirzepatide dose up to 15 mg in patients with T2DM with established CV disease and elevated risk for MACE. A Phase 3 Study 18F-MC-GPIJ is ongoing to investigate the reduction of morbidity and mortality with once-weekly tirzepatide treatment compared with placebo in adult participants living with obesity and established CV disease or CV risk factors, excluding diabetes.
Immunocompromised patients	Tirzepatide has not been specifically studied in immunocompromised patients.
Patients with a disease severity different from inclusion criteria in clinical trials	The clinical development programme included a representative population of: • patients with different degrees of T2DM severity defined by inclusion criteria, such as baseline HbA1c, duration of diabetes, and use of other diabetes medications. • patients with different degrees of overweight/obesity defined by BMI criteria.
Population with relevant different ethnic origin	Patients with diabetes and overweight/obesity from different racial and ethnic backgrounds were included in the tirzepatide clinical development programme. The number of patients and exposure time are shown in Table SIII.7.to Table SIII.10.
Subpopulations carrying relevant genetic polymorphisms	In the CWM clinical trials, those with known or suspected monogenetic or syndromic obesity were excluded. However, a study is under development to investigate the relationship between response to tirzepatide in the CWM trials and genetic variants thought to play a role in obesity.
Other	Not applicable.

Abbreviations: BMI = body mass index; CKD = chronic kidney disease; CV = cardiovascular; CWM = chronic weight management; eGFR = estimated glomerular filtration rate; HbA1c = glycosylated haemoglobin A1c; MACE = major adverse cardiovascular events; PK = pharmacokinetics; PD = pharmacodynamics; T2DM = type 2 diabetes mellitus.

Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

Post-authorisation data for calculating exposure are not yet available.

SV.1.1 Method Used to Calculate Exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 - Potential for Misuse for Illegal Purposes

The potential for misuse of tirzepatide for illegal purposes (as defined in Annex I of Guideline on Good Pharmacovigilance Practices) (EMA 2017) is not considered to be a significant risk.

Neither tirzepatide, nor any drug in a related pharmacologic class has a known profile as a drug of abuse. There were no reported instances of intended drug abuse in the tirzepatide clinical programme.

Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- not applicable.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- not applicable.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

- hypoglycaemia (in participants with T2DM only),
- hypersensitivity, and
- acute pancreatitis.

Known risks that do not impact the risk-benefit profile:

- not applicable.

Other reasons for considering the risks not important:

- not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: None

Risk-Benefit Impact:
Not applicable.

Important Potential Risk 1: Medullary thyroid cancer

Risk-Benefit Impact

Medullary thyroid cancer is a rare cancer that accounts for 2% to 4% of all thyroid cancers, with a 5-year survival of 80%. It may result in associated costs with hospitalisation, surgery, and morbidity (Schmid et al. 2015).

In nonclinical studies, thyroid C-cell tumours have been reported in rodents treated with some long-acting GLP-1 RAs. Treatment-related increases in thyroid C-cell hyperplasia and neoplasia were observed with tirzepatide, at all doses, in a 2-year rat carcinogenicity study. The relevance of rodent thyroid tumours to humans is not known. Nonclinical experience supports that the rodent thyroid C-cells are more sensitive to the effects of GLP-1 agonists than monkey thyroid C-cells. Clinical data have not demonstrated an apparent effect of GLP-1 agonists on C-cells in humans, and no cases of MTC or other C-cell disease have been reported in the completed tirzepatide clinical trial programme.

Neither a pharmacologically plausible mechanism linking the rodent findings to humans nor a causal relationship between tirzepatide and thyroid C-cell tumours has been established. At this time, there is insufficient evidence to attribute human thyroid C-cell disease to tirzepatide. Given the latency for cancer, the database for tirzepatide is of insufficient size and exposure duration to assess definitively for risk of any particular type of cancer.

MTC, if established, would impact the benefit/risk ratio of tirzepatide due to the medically important condition. To evaluate the potential association, a medullary thyroid carcinoma surveillance study (PASS Category 3) is planned to systematically monitor the annual incidence of medullary thyroid carcinoma as well as to identify any increase related to tirzepatide. This study is an additional pharmacovigilance activity and will be conducted similar to studies with other long-acting medicinal products in the GLP-1 RA class (Part III.2).

Important Potential Risk 2: Pancreatic malignancy

Risk-benefit impact:
Pancreatic cancer is a rare cancer with a low rate of survival. Should a causal association be determined between tirzepatide and pancreatic carcinoma, the benefit versus risk ratio would be reduced.

Nonclinical data for tirzepatide did not suggest any mutagenicity or genotoxicity. The nonclinical data were generally similar to the data for marketed GLP-1 RAs and did not identify any evidence of pancreatitis or pancreatic cancer. Promotion of tumours by long-acting GLP-1 RAs has been proposed as a concern for these treatments because of their action to chronically stimulate GLP-1 receptors, particularly in thyroid C-cells and the pancreas (Bjerre Knudsen et al. 2010; Butler et al. 2010).

In the completed Phase 2 and Phase 3 studies for tirzepatide, the incidence and exposure-adjusted incidence (defined as number of patients with events/observation time [person-years] × 100) of pancreatic malignancy are low: 0.04% and 0.04 patients/100

person-years, respectively, for T2DM, and 0.02% and 0.02 patients/100 person-years, respectively, for CWM.

There is no evidence from clinical trials that GLP-1-based therapies increase the risk of pancreatic cancer, although causality is suspected for the long-acting GLP-1 RAs from nonclinical studies. Given the latency for cancer, the database for tirzepatide is of insufficient size and exposure duration to assess definitively for risk of any particular type of cancer, especially for slow developing pancreatic cancer.

Pancreatic malignancy, if established, would impact the benefit/risk ratio of tirzepatide due to the clinical importance of pancreatic cancer. Pancreatic cancer develops slowly, and the currently available data do not allow for the assessment of the association with tirzepatide. To confirm or refute this association, a pancreatic malignancy surveillance study (PASS Category 3) is planned to systematically monitor the annual incidence as well as to identify any increase related to tirzepatide (Part III.2).

Important Potential Risk 3: Diabetic retinopathy complications

Risk-benefit impact:
Tirzepatide provides clinically meaningful improvement in glycaemic control, which is beneficial in reducing the risk of DR complications. However, it has been suggested that rapid glycaemic improvement may lead to temporary worsening of DR and associated complications.

Patients with a history of proliferative DR, diabetic maculopathy, or non-proliferative DR planned treatment were excluded from the tirzepatide clinical trial development programme. The current tirzepatide clinical trial data do not support a causal association with DR complications. Per clinical trial data, the incidence and exposure-adjusted incidence (defined as number of patients with events/total observation time [person-years] × 100) of DR in completed clinical trials for tirzepatide are low: 0.35% and 0.33 patients/100 person-years, respectively.

DR complications, if established, would impact the benefit/risk ratio of tirzepatide due to the medically important condition of DR complications. However, the currently available data do not allow for the evaluation of the association since patients with a history of DR complications were excluded from the tirzepatide clinical trial development programme. To confirm or refute this association, the risk of disease progression for DR among patients treated with tirzepatide is being further assessed in an ongoing addendum study, Protocol addendum I8F-MC-GPGN (GPGN) (7) (Part III.2).

Missing Information: Use in pregnancy and lactation

Risk-benefit impact:
Tirzepatide has not been tested in pregnant and breastfeeding women. There are no plans to include pregnant or breastfeeding women in future trials. Studies in animals have shown that developmental effects (reduced foetal weights and increased numbers of malformations and developmental variations) occurred in conjunction with pharmacological effects on maternal weight and food consumption. Therefore, the use of tirzepatide is not recommended during pregnancy.

It is unknown whether tirzepatide is excreted in breast milk. A risk to new-borns or infants cannot be excluded. Tirzepatide should be used with caution during breastfeeding.

At present, the impact on the benefit-risk balance of tirzepatide is unknown.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: None

Important Potential Risk: Medullary thyroid cancer

Potential mechanisms

No causal relationship has been established between GLP-1 RA administration and MTC in humans. Evidence linking MTC to treatment with tirzepatide and other products in the incretin-based therapies is entirely from nonclinical studies. Expression levels of GLP-1 receptor on thyroid C-cells differs across species, with rats having high expression levels, while humans and cynomolgus monkeys have low expression levels. Receptor expression in rats and mouse thyroid glands show a density that is 22- and 45-fold higher than that reported for humans and cynomolgus monkeys, respectively (Bjerre Knudsen et al. 2010; Waser et al. 2011). Furthermore, rats have been shown to be more sensitive to the effects of GLP-1 RAs than monkeys (Bjerre Knudsen et al. 2010; Vahle et al. 2015). Thus, the weight of evidence suggests that the observation in rodents might not have relevance in humans.

Evidence source(s) and strength of evidence:

In nonclinical studies, treatment-related increases in thyroid C-cell hyperplasia and neoplasia were observed with tirzepatide, at all doses, in a 2-year rat carcinogenicity study. The relevance of rodent thyroid tumours to humans is not known. This effect on rodent thyroids has been observed consistently with other long-acting GLP-1 RAs, including liraglutide, exenatide once

weekly, dulaglutide, and semaglutide, in near-lifetime exposure carcinogenicity studies. The relevance to humans cannot be determined from clinical and nonclinical studies. At this time, there is insufficient evidence to attribute thyroid C-cell disease to tirzepatide. Given the latency for cancer, the database for tirzepatide is of insufficient size and exposure duration to assess definitively for risk of any particular type of cancer.

Characterisation of the risk:

Nonclinical data suggest that this safety concern is a key safety finding. However, there were no cases of MTC, or other C-cell disease reported in the completed tirzepatide clinical trial programme.

Risk factors and risk groups:

Medullary thyroid carcinoma develops from C (parafollicular) cells and accounts for 5% to 10% of all thyroid cancers (Brady 2018), and up to 25% of MTC cases develop under multiple endocrine neoplasia-2A (IARC 2018). Compared to the general population (6.6%), patients with diabetes have a higher prevalence of thyroid disorders (10.8%) (Shih et al. 2012). However, the link between T2DM and thyroid cancer is arguable. Some studies did not show an association between diabetes, including T2DM and thyroid cancer risk (Kitahara et al. 2012; Shih et al. 2012; Seo et al. 2017). Other studies showed that patients with diabetes are 20% to 34% more likely to develop thyroid cancer compared to those without diabetes (Yeo et al. 2014; Li and Qian 2017).

Studies show that the risk of thyroid cancer, specifically papillary thyroid cancer, increased in participants with overweight and obesity compared with normal-weight participants. It has been estimated that a 5-point increase in BMI and a 0.1-point increase in waist-to-hip ratio increase the risk of thyroid cancer by 30% and 14%, respectively (Schmid et al. 2015, Kitahara et al. 2020, Li et al. 2020). Although there is a positive association between obesity/overweight and papillary, follicular, and anaplastic thyroid cancers, there was an inverse association noted with MTC (Schmid et al. 2015).

Preventability:The only known risk factors are genetic in nature. In the US, GLP-1 RAs are contraindicated in patients with a personal or family history of MTC or multiple endocrine neoplasia type 2. It is unknown if this precautionary measure prevents MTC from developing in patients with a family history of MTC or multiple endocrine neoplasia type 2. (Schmid et al. 2015).

Impact on the risk-benefit balance of the product:

In general, thyroid cancer is a rare condition. Medullary thyroid cancer is a rare cancer that accounts for 2% to 4% of all thyroid cancers, with a 5-year survival of 80%. It may result in associated costs with hospitalisation, surgery, and morbidity (Schmid et al. 2015).

In nonclinical studies, thyroid C-cell tumours have been reported in rodents treated with some long-acting GLP-1 RAs. Treatment-related increases in thyroid C-cell hyperplasia and neoplasia were observed with tirzepatide, at all doses, in a 2-year rat carcinogenicity study. The relevance

of rodent thyroid tumours to humans is not known. Nonclinical experience supports that the rodent thyroid C-cells are more sensitive to the effects of GLP-1 agonists than monkey thyroid C-cells. Clinical data have not demonstrated an apparent effect of GLP-1 agonists on C-cells in humans, and no cases of MTC or other C-cell disease reported in the tirzepatide clinical trial programme.

Neither a pharmacologically plausible mechanism linking the rodent findings to humans nor a causal relationship between tirzepatide and thyroid C-cell tumours has been established. At this time, there is insufficient evidence to attribute human thyroid C-cell disease to tirzepatide. Given the latency for cancer, the database for tirzepatide is of insufficient size and exposure duration to assess definitively for any particular type of cancer.

MTC, if established, would impact the benefit/risk ratio of tirzepatide due to the medically important condition. To evaluate the potential association, a medullary thyroid carcinoma surveillance study (PASS Category 3) is planned to systematically monitor the annual incidence of medullary thyroid carcinoma as well as to identify any increase related to tirzepatide. This study is an additional pharmacovigilance activity and will be conducted similar to studies with other long-acting medicinal products in the GLP-1 RA class (Part III.2).

Public health impact:
There were no cases of MTC, or other C-cell disease reported in the completed tirzepatide clinical trial programme. A link between treatment with tirzepatide and the occurrence of MTC has not been established in humans.

Based on the assumption that only a pre-existent MTC might be stimulated to grow by a GLP-1 RA, then, even a confirmed link between GLP-1 RA and this rare thyroid tumour would have very limited impact on public health.

Important Potential Risk: Pancreatic malignancy

Potential mechanisms:

Nonclinical data for tirzepatide did not suggest any mutagenicity or genotoxicity and were generally similar to marketed GLP-1 RAs and did not identify evidence of pancreatitis or pancreatic cancer. Promotion of tumours by long-acting GLP-1 RAs has been proposed as a concern for these treatments because of their action to chronically stimulate GLP-1 receptors, particularly in thyroid C-cells and the pancreas (Bjerre Knudsen et al. 2010; Butler et al. 2010).

Evidence source(s) and strength of evidence:

There is no evidence from clinical trials that GLP-1-based therapies increase the risk of pancreatic cancer. Some reports indicate a causal association with these agents, while others have failed to show such an association. A joint US Food and Drug Administration and EMA publication states that, data demonstrate conflicting opinions about the strength of the association (Egan et al. 2014).

To date, no causal relationship between tirzepatide and pancreatic malignancy has been established. From the Phase 2 and 3 clinical trial programmes for tirzepatide, a few cases of

pancreatic malignancy were reported. There were 4 cases of pancreatic cancer, of which 2 were from tirzepatide groups and 2 from placebo group.

Characterisation of the risk:

Data source: Completed Phase 2 and 3 studies (all tirzepatide doses and exposure)

- Incidence: 0.02% (2 out of 8780 tirzepatide-treated participants)
- Exposure-adjusted incidence[a]: 0.02 participants/100 person-years (total observation time: 8219.5 person-years)

[a] Exposure-adjusted incidence is calculated as n/total observation time [person-years] × 100, where n = number of patients with events.

Risk factors and risk groups:

Patients with long-standing T2DM are twice more likely to have pancreatic cancer than patients without T2DM. About 0.5% of patients who were newly diagnosed with T2DM develop pancreatic cancer within 6 years of follow-up (Yadav and Lowenfels 2013).

Obesity increases the risk of pancreatic cancer, with approximate 10% or greater increases in risk of pancreatic cancer for a 5 kg/m^2 unit increase in BMI, or a 20% to 50% increased risk among those with obesity relative to participants with normal BMI (Berrington et al. 2003; Larsson et al. 2007; Renehan et al. 2008).

Being the fourth leading cause of cancer mortality, pancreatic cancer is a highly mortal malignancy with 75% of patients dying within the first year of diagnosis (Bracci 2012). The 5-year survival rate among patients with pancreatic malignancy is about 6% (Yadav and Lowenfels 2013).

Preventability:

The risk of pancreatic malignancy cannot be mitigated sufficiently. Symptoms and signs, once present, often relate to advanced disease (McAuliffe and Christein 2013). Among the major risk factors associated with pancreatic malignancy, about 66% are potentially modifiable, including smoking cessation, limiting alcohol consumption, and adopting healthy diet and lifestyle. These behaviours could reduce pancreatic malignancy risk by 30% (Maisonneuve and Lowenfels 2018).

Impact on the risk-benefit balance of the product:

Pancreatic cancer is a rare cancer with a low rate of survival. It may reduce the benefit versus risk ratio.

Nonclinical data for tirzepatide did not suggest any mutagenicity or genotoxicity. The nonclinical data were generally similar to the data for marketed GLP-1 RAs and did not identify any evidence of pancreatitis or pancreatic cancer. Promotion of tumours by long-acting GLP-1 RAs has been proposed as a concern for these treatments because of their action to chronically stimulate GLP-1 receptors, particularly in thyroid C-cells and the pancreas (Bjerre Knudsen et al. 2010; Butler et al. 2010).

In the completed Phase 2 and Phase 3 studies for tirzepatide, the incidence and exposure-adjusted incidence (defined as number of patients with events/observation time [person-years] × 100) of pancreatic malignancy in completed clinical trials for tirzepatide are low: 0.04%, 0.04 patients/100 person-years respectively.

There is no evidence from clinical trials that GLP-1-based therapies increase the risk of pancreatic cancer, although causality is suspected for the long-acting GLP-1 RAs in nonclinical studies. Given the latency for cancer, the database for tirzepatide is of insufficient size and exposure duration to assess definitively for any particular type of cancer, especially for slow developing pancreatic cancer.

Pancreatic malignancy, if established, would impact the benefit/risk ratio of tirzepatide due to the clinical importance of pancreatic cancer. Pancreatic cancer develops slowly, and the currently available data do not allow for the assessment of this association with tirzepatide. To confirm or refute this association, a pancreatic malignancy surveillance study (PASS Category 3) is planned to systematically monitor the annual incidence as well as to identify any increase related to tirzepatide (Part III.2).

Public health impact:

Given the very low incidence of pancreatic cancers observed in patients treated with tirzepatide and the uncertainties regarding a causal association, the public health impact is considered to be negligible at this time.

Important Potential Risk: Diabetic retinopathy complications

Potential mechanisms:

DR is a microvascular complication of diabetes caused by damage to the retinal blood vessels. Control of blood glucose level has been shown to reduce the risk of new onset DR and slow the long-term progression of existing DR (Diabetes Control and Complications Trial Group 1993; UKPDS 1998). Rapid improvement in glucose control has been associated with an early and temporary worsening of DR in patients with diabetes (Lauritzen 1983, 1985; Diabetes Control and Complications Trial Research Group 1998; Shurter et al. 2013; Fullerton et al. 2014; Bain et al. 2019). Intensive glycaemic control and fast robust blood glucose reduction on GLP-1 receptor agonists and potentially on tirzepatide, similar to insulins, could result in faster progression of DR in the initial phase of the treatment in patients with proliferative DR, macular oedema, or both.

Evidence source(s) and strength of evidence:

Worldwide, the prevalence of DR ranges between 10% and 61% (median 28%) among patients with T2DM and between 1.5% and 31% (median 11%) among those newly diagnosed with T2DM (Ruta et al. 2013). The incidence rates of DR among adults aged 30 years and older with T2DM in the UK and Spain were 11.6 and 81.3 per 1000 people, respectively (Thomas et al. 2012; Romero-Aroca et al. 2017).

Deterioration of DR among patients with improved glycaemic control is documented with limited information for patients with T2DM specifically (Hooymans et al. 1982; Yau et al. 2012; Bain et al. 2019). A study conducted by Oslo Study Group-Brinchmann-Hansen et al. reported worsening of DR after introduction of stringent diabetes management within 3 months of treatment; approximately 50% of treated patients were affected compared with none of the patients treated conventionally (Oslo Study Group et al. 1985). A study conducted among patients with type 2 diabetes reported that the risk of progression of DR after 3 and 9 years was 15.8% and 23%, respectively, for patients treated with intensive therapy compared with 15.3% and 27.8%, respectively, for patients undergoing treatment with either insulin or a sulphonylurea (Bain et al. 2019). A meta-analysis of 4 randomised controlled trials reported that after 5 years of follow-up, more intensive glucose control was associated with a 13% reduction of eye events (risk ratio: 0.87; 95% confidence interval: 0.76, 1.00; p = 0.04; Feldman-Billard et al. 2018).

Patients with a history of proliferative DR, diabetic maculopathy, or non-proliferative DR that required acute treatment were excluded from the tirzepatide clinical trial development programme. A dedicated retinopathy addendum to SURPASS-CVOT I8F-MC-GPGN is ongoing, which will further investigate the risk of disease progression for DR among patients treated with tirzepatide. The comparative analysis of the worsening of an existing DR with other diabetic treatment to tirzepatide treatment will be conducted after the addendum GPGN sub-study results are available.

Therefore, there was limited experience to determine whether the safety profile in this patient population is different from that expected in the population without DR. In Phase 3 clinical trials, a dilated fundoscopic examination was performed at baseline and when clinically indicated by any suspected adverse event of worsening retinopathy or clinically recommended during the course of the study. Incidence rate for patients with DR complications was 0.35%.

Characterisation of the risk:

Data source: Completed Phase 3 studies (all tirzepatide doses)

- Incidence*: 0.35% (18 patients out of 5119 tirzepatide-treated patients)
- Exposure-adjusted incidence[a]: 0.33 patients/100 person-years (total observation time: 5441.76 person-years)

* Incidence rate is calculated as the number of patients with DR complications (onset or worsening) recorded on the retinopathy electronic case report form/number of subjects in Phase 3 Dose Effect Analysis Set.

[a] Exposure-adjusted incidence is calculated as n/total observation time [person-years] × 100, where n = number of patients with events.

Risk factors and risk groups:

Patients with T2DM are at a risk of developing microvascular complications, including DR, nephropathy, and neuropathy. Rapid improvement in glucose control has been associated with an early and temporary worsening of DR in patients with diabetes (Lauritzen 1983, 1985; Diabetes Control and Complications Trial Research Group 1998; Shurter et al. 2013; Fullerton et al. 2014; Bain et al. 2019).

Modifiable risk factors for DR include high blood glucose, high blood pressure, high serum lipids, and smoking. Non-modifiable risk factors include diabetes duration, age, race, and genetic predisposition (Ding and Wong 2012; Scanlon et al. 2013).

Preventability:

Long-term control of blood glucose has been shown to reduce the risk of new onset DR and slow the progression of existing DR. In addition to the long-term glucose control, it is important for patients to attend their annual diabetic appointment, as this can be an opportunity to detect early signs of eye problems.

Early detection of retinopathy increases the chances of the treatment being effective and preventing it from getting worse (NHS 2021). Patients should have their eyes examined regularly and inform their doctor of any changes in their eyesight.

Impact on the risk-benefit balance of the product:

Tirzepatide provides clinically meaningful improvement in glycaemic control, which is beneficial in reducing the risk of DR complications. However, it has been suggested that rapid glycaemic improvement may lead to temporary worsening of DR and associated complications.

Patients with a history of proliferative DR, diabetic maculopathy, or non-proliferative DR with planned treatment were excluded from the tirzepatide clinical trial development programme. The current tirzepatide clinical trial data do not support a causal association with DR complications. Per clinical trial data, the incidence and exposure-adjusted incidence (defined as number of patients with events/total observation time [person-years] × 100) of DR in completed clinical trials for tirzepatide are low: 0.35% and 0.33 patients/100 person-years, respectively.

DR complications, if established, would impact the benefit/risk ratio of tirzepatide due to the medically important condition of DR complications. However, the currently available data do not allow for the evaluation of this association since patients with a history of DR complications were excluded from the tirzepatide clinical trial development programme. To confirm or refute this association, the risk of disease progression for DR among patients treated with tirzepatide is being further assessed in an ongoing addendum study, Protocol addendum I8F-MC-GPGN (7) (Part III.2).

Public health impact:

Given the low incidence of DR outcome observed in patients treated with tirzepatide, the public health impact is considered low at this time.

SVII.3.2 Presentation of the Missing Information

Missing Information: Use in pregnancy and lactation

Evidence source:

Consistent with the standard practice in clinical development, pregnant women, breastfeeding women, or both were excluded from the clinical trial development programme. Hence, there were only limited data on the use of tirzepatide in pregnant women, breastfeeding women, or both. During the tirzepatide clinical trial programme, 0.13% of women exposed to tirzepatide became pregnant.

Anticipated risk/consequence of the missing information:

Tirzepatide has not been tested in pregnant and breastfeeding women. There are no plans to include pregnant or breastfeeding women in future trials. Studies in animals have shown that developmental effects (reduced foetal weights and increased numbers of malformations and developmental variations) occurred in conjunction with pharmacological effects on maternal weight and food consumption. Therefore, the use of tirzepatide is not recommended during pregnancy.

It is unknown whether tirzepatide is excreted in breast milk. A risk to newborns or infants cannot be excluded. Tirzepatide should be used with caution during breastfeeding.

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Medullary thyroid cancer Pancreatic malignancy Diabetic retinopathy complications
Missing information	Use in pregnancy and lactation

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

Routine follow-up will be conducted on events of special interest**:**

- Medullary thyroid cancer
  - Hypocalcaemia, hypokalaemia, hypomagnesaemia, hypophosphataemia follow-up form
  - Cancer/neoplasm follow-up form
- Pancreatic malignancy
  - Cancer/neoplasm follow-up form

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 Additional Pharmacovigilance Activities

A database linkage study to evaluate the important potential risk of MTC (I8F-MC-B013)

Study short name and title:
A Medullary Thyroid Carcinoma Database Linkage Study (I8F-MC-B013)

Rationale and draft study objectives:
This is an observational database study using a matched cohort design. This study addresses the important potential risk of MTC observed in rodents across all GLP-1 RAs.
The study objectives are as follows:

- primary objective is to estimate the incidence of MTC among patients who are exposed to GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, as compared to an unexposed matched comparator cohort using incidence rate ratios and 95% CIs.

The secondary objectives are to

- systematically monitor the annual incidence of MTC in adults (18 years of age and older) in the US for identification of any possible increase related to the introduction of GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, into the US market, and
- characterise patients exposed to GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, and unexposed matched comparator cohorts using demographic characteristics and other clinical characteristics, selected prescription medications dispensed during the baseline period, and duration of GLP-1 RA (including GIP/GLP-1 RA) use.

Study design:

An observational database study using a matched cohort design.

Study population:
Patients aged 18 years and older with a pharmacy-dispensed prescription with incretin-based therapies, including GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, compared to unexposed cohorts.

Milestones:
Draft Protocol outline was submitted on 20 January 2023.

Tirzepatide Pancreatic Malignancy Study (I8F-MC-B011)
Study short name and title:
Tirzepatide Pancreatic Malignancy Study (I8F-MC-B011)

Rationale and study objectives:
The study objectives are as follows:

- This study aims to evaluate the incidence of pancreatic cancer in association with tirzepatide
- treatment compared to patients unexposed to tirzepatide.

The primary objectives of this study are to

- estimate the incidence rate of pancreatic cancer among new users of tirzepatide
- compare the incidence rate of pancreatic cancer among new users of tirzepatide to patients who are new users of other incretin-based therapies, and
- compare the incidence rate of pancreatic cancer among new users of tirzepatide to patients who are new users of non-incretin-based therapies.

The secondary objective of this study is to describe baseline characteristics (including demographics, lifestyle variables, medical conditions, and medications) among patients who are new users of tirzepatide and patients who are new users of other incretin-based therapies and non-incretin-based therapies.

This study will address the important potential risk of pancreatic malignancy.

Study design:
Retrospective non-interventional cohort study.

Study population:
Patients aged 18 years and older who have newly been dispensed GLP-1 RAs and the GIP/GLP-1 RA tirzepatide incretin-based therapies for the exposed cohort and for the comparators, other newly dispensed incretin-based therapies or non-incretin-based therapies.

Milestones:
Draft Protocol outline was submitted on 20 January 2023.

Retinopathy addendum to SURPASS-CVOT (I8F-MC-GPGN)

Study short name and title:
Retinopathy addendum to SURPASS-CVOT (I8F-MC-GPGN)

Rationale and study objectives:
The study objective is

- to compare the effect of tirzepatide dose up to 15 mg QW with dulaglutide 1.5 mg QW on DR progression.
- to assess the safety of tirzepatide dose up to 15 mg QW when compared with dulaglutide 1.5 mg QW on DR.

This study will address the safety concerns of DR complications.

Study design:
This addendum is to be performed in addition to all procedures required by Protocol I8F-MC-GPGN or any subsequent amendments to that protocol.

Study population:
Patient can qualify based on the presence of any severity of DR, macular oedema, or both described during the ophthalmology assessment at screening.

Milestones:
Estimated submission of study report: within 6 months after the clinical study report approval (estimated date of clinical study report approval: 04/01/2025).

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Category 2 – Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Category 3 - Required additional pharmacovigilance activities				
Medullary Thyroid Carcinoma Database Linkage Study (I8F-MC-B013) Planned	The primary objective is • to estimate the incidence of among patients who are exposed to GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, as compared to an unexposed matched comparator cohort using incidence rate ratios and 95% CI. The secondary objectives are to • systematically monitor the annual incidence of MTC in adults (18 years of age and older) in the US for identification of any possible increase related to the introduction of GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, into the US market, and • characterise patients exposed to GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, and unexposed matched comparator cohorts using demographic characteristics and other clinical characteristics, selected prescription medications dispensed during the baseline period, and duration of GLP-1 RA (including GIP/GLP-1 RA) use.	Important potential risk of medullary thyroid cancer	Submission of draft protocol outline	Draft protocol outline was submitted to on 20 January 2023.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Tirzepatide Pancreatic Malignancy Study (I8F-MC-B011) Planned	The primary objectives of this study are • to estimate the incidence rate of pancreatic cancer among new users of tirzepatide • to compare the incidence rate of pancreatic cancer among new users of tirzepatide to patients who are new users of other incretin-based therapies, and • compare the incidence rate of pancreatic cancer among new users of tirzepatide to patients who are new users of non-incretin-based therapies. The secondary objective of this study is to describe baseline characteristics (including demographics, lifestyle variables, medical conditions, medications) among patients who are new users of tirzepatide and patients who are new users of other incretin-based therapies and non-incretin-based therapies.	Important potential risk of pancreatic malignancy	Submission of draft protocol outline	Draft protocol outline was submitted on 20 January 2023.
Retinopathy addendum to SURPASS-CVOT Study (I8F-MC-GPGN) Ongoing	To compare the effect of tirzepatide dose up to 15 mg QW with dulaglutide 1.5 mg QW on DR progression. To assess the safety of tirzepatide dose up to 15 mg QW when compared with dulaglutide 1.5 mg QW on DR.	Important potential risk of DR complications	Protocol submission	Provided in Annex 3 of this RMP
			Submission of CSR	Within 6 months after CSR approval (estimated CSR approval date: 04/01/2025)

Abbreviations: CHMP = Committee for Medicinal Products for Human Use; CSR = clinical study report; DR = diabetic retinopathy; GLP-1 = glucagon-like peptide-1; MTC = medullary thyroid cancer; QW = once weekly; RA = receptor agonist; RMP = risk management plan

Part IV: Plans for Post-Authorisation Efficacy Studies

Table Part IV.1. Planned and Ongoing Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorisation				
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Efficacy studies that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine Risk Minimisation Activities
Important Potential Risks	
Medullary thyroid cancer	**Routine risk communication:** • SmPC Section 5.3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Not applicable **Other routine risk minimisation measures beyond the Product Information:** **Pack size:** • Not applicable **Legal status:** Not applicable
Pancreatic malignancy	**Routine risk communication:** • Not applicable **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Not applicable **Other routine risk minimisation measures beyond the Product Information:** **Pack size:** • Not applicable **Legal status:** • Not applicable
Diabetic retinopathy complications	**Routine risk communication:** • SmPC Section 4.4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Not applicable **Other routine risk minimisation measures beyond the Product Information:** **Pack size:** • Not applicable **Legal status:** • Not applicable

Safety concern	Routine Risk Minimisation Activities
Missing information	
Use in pregnant and/or breastfeeding women	**Routine risk communication:** • SmPC Section 4.6 • PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Section 4.6 advises that the use of tirzepatide is not recommended during pregnancy. It is unknown whether tirzepatide is excreted in breast milk. A risk to newborns or infants cannot be excluded. Tirzepatide should be used with caution during breastfeeding. **Other routine risk minimisation measures beyond the Product Information:** **Pack size:** • Not applicable **Legal status:** • Not applicable

Abbreviations: PL = package leaflet; SmPC = Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Potential Risks		
Medullary thyroid cancer	**Routine risk minimisation measures:** • SmPC Section 5.3 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: • Cancer/Neoplasm follow-up form • Hypocalcaemia, Hypokalaemia, Hypomagnesaemia, Hypophosphataemia follow-up form **Additional pharmacovigilance activities:** I8F-MC-B013: A Medullary Thyroid Carcinoma Database Linkage Study: The primary objective to estimate the incidence of medullary thyroid carcinoma among patients who are exposed to GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, as compared to an unexposed matched comparator cohort using incidence rate ratios and 95% CI. The secondary objectives are to • systematically monitor the annual incidence of MTC in adults (18 years of age and older) in the US for identification of any possible increase related to the introduction of GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, into the US market, and • characterise patients exposed to GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, and unexposed matched comparator cohorts using demographic characteristics and other clinical characteristics, selected prescription medications dispensed during the baseline period, and duration of GLP-1 RA (including GIP/GLP-1 RA) use.
Pancreatic malignancy	**Routine risk minimisation measures:** • None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: • Cancer/Neoplasm follow-up form **Additional pharmacovigilance activities:** • I8F-MC-B011: Tirzepatide Pancreatic Malignancy Study: This is a retrospective non-interventional cohort study.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		The primary objectives of this study are to • estimate the incidence rate of pancreatic cancer among new users of tirzepatide • compare the incidence rate of pancreatic cancer among new users of tirzepatide to patients who are new users of other incretin-based therapies, and • compare the incidence rate of pancreatic cancer among new users of tirzepatide to patients who are new users of non-incretin-based therapies. The secondary objective of this study is to describe baseline characteristics (including demographics, lifestyle variables, medical conditions, medications) among patients who are new users of tirzepatide and patients who are new users of other incretin-based therapies and non-incretin-based therapies.
Diabetic retinopathy complications	**Routine risk minimisation measures:** • SmPC Section 4.4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Not applicable **Additional pharmacovigilance activities:** • Protocol Addendum I8F-MC-GPGN This is a retinopathy addendum to SURPASS-CVOT (I8F-MC-GPGN) to compare the effect of tirzepatide dose up to 15 mg QW with dulaglutide 1.5 mg QW on DR progression. and to assess the safety of tirzepatide dose up to 15 mg QW when compared with dulaglutide 1.5 mg QW on DR.
Missing Information		
Use in pregnant and/or breastfeeding women	**Routine risk minimisation measures:** • SmPC Section 4.6 • PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Not applicable **Additional pharmacovigilance activities:** • None

Abbreviations: GLP-1 = glucagon-like peptide-1; MTC = medullary thyroid cancer; PL = package leaflet; RA = receptor agonist; SmPC = Summary of Product Characteristics.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Mounjaro (Tirzepatide)

This is a summary of the RMP for Mounjaro. The RMP details important risks of Mounjaro, how these risks can be minimised, and how more information will be obtained about Mounjaro's risks and uncertainties (missing information).

Mounjaro's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Mounjaro should be used.

This summary of the RMP for Mounjaro should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Mounjaro's RMP.

I - The Medicine and What It is Used for

Mounjaro is authorised for T2DM (see SmPC for the full indication). It contains tirzepatide as the active substance and it is given by injection.

Further information about the evaluation of Mounjaro's benefits can be found in Mounjaro's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

Mounjaro is indicated as an adjunct to a reduced-calorie diet and increased physical activity for CWM, including weight loss and weight maintenance, in adults with an initial BMI of

- ≥30 kg/m^2 (obesity) or
- ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition (e.g., hypertension, dyslipidemia, obstructive sleep apnoea, CV disease, prediabetes, or T2DM.

It contains tirzepatide as the active substance and is given by injection.

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Mounjaro, together with measures to minimise such risks and the proposed studies for learning more about Mounjaro's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be

- specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- important advice on the medicine's packaging
- the authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly, and

- the medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Mounjaro is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Mounjaro are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Mounjaro. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Medullary thyroid cancer Pancreatic malignancy Diabetic retinopathy complications
Missing information	Use in pregnancy and lactation

II.B Summary of Important Risks

Important potential risk: Medullary thyroid cancer	
Evidence for linking the risk to the medicine	In nonclinical studies, treatment-related increases in thyroid C-cell hyperplasia and neoplasia were observed with tirzepatide, at all doses, in a 2-year rat carcinogenicity study. This effect on rodent thyroids has been observed consistently with other long-acting GLP-1 RAs, including liraglutide, exenatide once weekly, dulaglutide, and semaglutide, in near-lifetime exposure carcinogenicity studies. The relevance to humans cannot be determined from clinical and nonclinical studies. At this time, there is insufficient evidence to attribute thyroid C-cell disease to tirzepatide. Given the latency for cancer, the database for tirzepatide is of insufficient size and exposure duration to assess definitively for any particular type of cancer. Nonclinical data suggest that there is a risk for MTC with tirzepatide, and this has been determined to be a key safety finding from the nonclinical development programme.
Risk factors and risk groups	Medullary thyroid carcinoma develops from the C (parafollicular) cells and accounts for 5% to 10% of all thyroid cancers (Brady 2018), and up to 25% of MTC cases develop under multiple endocrine neoplasia-2A (IARC 2018). Compared to the general population (6.6%), patients with diabetes have a higher prevalence of thyroid disorders (10.8%) (Shih et al. 2012). However, the link between T2DM and thyroid cancer is arguable. Some studies did not show an association between diabetes, including T2DM and thyroid cancer risk (Kitahara et al. 2012; Shih et al. 2012; Seo et al. 2017). Other studies showed that patients with diabetes are 20% to 34% more likely to develop thyroid cancer compared to those without diabetes (Yeo et al. 2014; Li and Qian 2017). Many studies show that the risk of thyroid cancer, specifically papillary thyroid cancer, increased in participants with overweight and obesity compared with normal-weight participants. It has been estimated that a 5-point increase in BMI and a 0.1-point increase in waist-to-hip ratio increase the risk of thyroid cancer by 30% and 14%, respectively (Schmid et al. 2015; Kitahara et al. 2020; Li et al. 2020). Although there is a positive association between obesity/overweight and papillary, follicular, and anaplastic thyroid cancers, there was an inverse association noted with MTC (Schmid et al. 2015).
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 5.3 **Additional risk minimisation measures:** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • I8F-MC-B013: A Medullary Thyroid Carcinoma database linkage study See Section Post-Authorisation Development Plan of this

	summary for an overview of the post-authorisation development plan.
Important potential risk: Pancreatic malignancy	
Evidence for linking the risk to the medicine	There is no evidence from clinical trials that GLP-1-based therapies increase the risk of pancreatic cancer. Some literature reports indicate a causal association with these agents, while others have failed to show such an association. A joint FDA and EMA publication states that data demonstrate conflicting opinions about strength of the association (Egan et al. 2014). To date, no causal relationship between tirzepatide and pancreatic malignancy has been established. Incidence of pancreatic malignancy was similar in the tirzepatide and placebo groups in the Phase 2 and 3 clinical trials for tirzepatide.
Risk factors and risk groups	Patients with long-standing T2DM are twice more likely to have pancreatic cancer than patients without T2DM (Yadav and Lowenfels 2013). About 0.5% of patients newly diagnosed with T2DM develop pancreatic cancer within 6 years of follow-up. Obesity increases risk of pancreatic cancer, with approximate 10% or greater increases in risk of pancreatic cancer for a 5 kg/m^2 unit increase in BMI, or a 20% to 50% increased risk among those with obesity relative to participants with normal BMI (Berrington et al. 2003; Larsson et al. 2007; Renehan et al. 2008). Being the fourth leading cause of cancer mortality, pancreatic cancer is a highly mortal malignancy, with 75% of patients dying within the first year of diagnosis (Bracci 2012). The 5-year survival rate among patients with pancreatic malignancy is about 6% (Yadav and Lowenfels 2013).
Risk minimisation measures	**Routine risk minimisation measures:** • None **Additional risk minimisation measures:** • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • I8F-MC-B011: Tirzepatide Pancreatic Malignancy Study See Section II.C Post-Authorisation Development Plan of this summary for an overview of the post-authorisation development plan.
Important potential risk: Diabetic retinopathy complications	
Evidence for linking the risk to the medicine	Worldwide, the prevalence of DR ranges between 10% and 61% (median 28%) among patients with T2DM and between 1.5% and 31% (median 11%) among those newly diagnosed with T2DM (Ruta et al. 2013). The incidence rates of DR among adults aged 30 years and older with T2DM in the UK and Spain were 11.6 and 81.3 per 1000 people, respectively (Thomas et al. 2012; Romero-

	Aroca et al. 2017). Deterioration of DR among patients with improved glycaemic control is well documented with limited information for patients with T2DM specifically (Hooymans et al. 1982; Yau et al. 2012; Bain et al. 2019). A study conducted by Oslo Study Group-Brinchmann-Hansen et al. reported worsening of DR after introduction of stringent diabetes management within 3 months of treatment; approximately 50% of treated patients were affected compared with none of the patients treated conventionally (Oslo Study Group et al. 1985). A study conducted among patients with type 2 diabetes reported the risk of progression of DR after 3 and 9 years was 15.8% and 23%, respectively, for patients treated with intensive therapy compared with 15.3% and 27.8%, respectively, for patients undergoing treatment with either insulin or a sulphonylurea (Bain et al 2019). A meta-analysis of 4 randomised controlled trials reported that after 5 years of follow-up, more intensive glucose control was associated with a 13% reduction of eye events (risk ratio: 0.87; 95% confidence interval: 0.76, 1.00; p = 0.04; Feldman-Billard et al. 2018). Patients with a history of proliferative DR, diabetic maculopathy, or non-proliferative DR that required acute treatment were excluded from the tirzepatide clinical trial development programme. A dedicated retinopathy addendum to SURPASS-CVOT I8F-MC-GPGN (GPGN) is ongoing, which will further investigate the risk of disease progression for DR among patients treated with tirzepatide. The comparative analysis of the worsening of an existing DR with other diabetic treatment to tirzepatide treatment will be conducted after the addendum GPGN sub-study results are available. Therefore, there was limited experience to determine whether the safety profile in this patient population is different from that expected in the population without DR. In Phase 3 clinical trials, a dilated fundoscopic examination was performed when clinically indicated by any suspected adverse event of worsening retinopathy or clinically recommended during the course of the study. Worsening of fundoscopic examination result was observed in 18 tirzepatide-treated patients (0.35%).
Risk factors and risk groups	Patients with T2DM are at risk of developing microvascular complications including DR, nephropathy, and neuropathy. Modifiable risk factors for DR include high blood glucose, high blood pressure, high serum lipids, and smoking. Non-modifiable risk factors include diabetes duration, age, race, and genetic predisposition (Ding and Wong 2012; Scanlon et al. 2013).
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 4.4

	Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Retinopathy addendum to SURPASS-CVOT (I8F-MC-GPGN) See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Use in pregnant and/or breastfeeding women	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 4.6 • PL Section 2 **Additional risk minimisation measures:** • None

Abbreviations: DR = diabetic retinopathy; EMA = European Medicines Agency; FDA = United States Food and Drug Administration; GLP-1 = glucagon-like peptide 1; MTC: medullary thyroid cancer; PL = package leaflet; RA = receptor agonist; SmPC = Summary of Product Characteristics; T2DM = type 2 diabetes mellitus.

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Mounjaro.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study short name: A Medullary Thyroid Carcinoma Database Linkage Study (I8F-MC-B013)

Purpose of the study: This is an observational database study using a matched cohort design. This study addresses the important potential risk of MTC observed in rodents across all GLP-1 RAs.

The primary objective is to estimate the incidence of medullary thyroid carcinoma among patients who are exposed to GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, as compared to an unexposed matched comparator cohort using incidence rate ratios and 95% CIs.

The secondary objectives are to

- systematically monitor the annual incidence of MTC in adults (18 years of age and older) in the US for identification of any possible increase related to the introduction of GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, into the US market, and
- characterise patients exposed to GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, and unexposed matched comparator cohorts using demographic characteristics and other clinical characteristics, selected prescription medications dispensed during the baseline period, and duration of GLP-1 RA (including GIP/GLP-1 RA) use.

Study short name: Tirzepatide Pancreatic Malignancy Study (I8F-MC-B011)

Purpose of the study: This is a retrospective non-interventional cohort study that will address the safety concerns of pancreatic malignancy.

The primary objectives of this study are to

- estimate the incidence rate of pancreatic cancer among new users of tirzepatide
- compare the incidence rate of pancreatic cancer among new users of tirzepatide to patients who are new users of other incretin-based therapies, and
- compare the incidence rate of pancreatic cancer among new users of tirzepatide to patients who are new users of non-incretin-based therapies.

The secondary objective of this study is to describe baseline characteristics (including demographics, lifestyle variables, medical conditions, medications) among patients who are new users of tirzepatide and patients who are new users of other incretin-based therapies and non-incretin-based therapies.

Study short name: Retinopathy addendum to SURPASS-CVOT (I8F-MC-GPGN)

Purpose of the study: This is a retinopathy addendum to SURPASS-CVOT (I8F-MC-GPGN) to be performed in addition to all procedures required by Protocol I8F-MC-GPGN or any subsequent amendments to that protocol.

The study objective is

- to compare the effect of tirzepatide dose up to 15 mg QW with dulaglutide 1.5 mg QW on DR progression.
- to assess the safety of tirzepatide dose up to 15 mg QW when compared with dulaglutide 1.5 mg QW on DR.

Part VII: Annexes

Annex **Page**

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Follow-up forms

Specific Adverse Event Follow-up Form	Event(s) Associated with the Form
Form #1 Hypocalcaemia, Hypokalaemia, Hypomagnesaemia, Hypophosphataemia	Medullary thyroid cancer
Form #2 Cancer/Neoplasm	Medullary thyroid cancer Pancreatic malignancy

Form #1 Hypocalcaemia hypokalaemia hypomagnesaemia hypophosphataemia

Eli Lilly and Company - Global Patient Safety **Case Number: .**

Spontaneous Follow-up Form

Reported Events: .

Date: _____ **Lilly Case #:** . *

Information Provided By: _____ **Signature/Initials:** _____ **Fax:** Lilly (US) Global Patient Safety - (866) 644-1697 DC 4027

Patient's Name or Initials: . **Patient's Birth Date or Age:** .

Gender:	**Race:**	**Weight:**	**Height:**
○ F ○ M ○ Unknown	○ Caucasian ○ Asian ○ Black ○ Other	○ lb ○ kg	○ in ○ cm

Reported Drug: _____

Lot/Control Number(if available): _____ Indication: _____

Dose: _____ Frequency: _____ Formulation: _____

Start Date: _____ Dose when event occured: _____ Route: _____

Drug D/C? ○ No ○ Yes Date D/C: _____ If Discontinued, did the event resolve? ○ Yes ○ No

Drug Restarted? ○ No ○ Yes Date Restarted: _____ If Restarted, did the event occur? ○ Yes ○ No

Hypocalcemia, Hypokalemia, Hypomagnesemia, Hypophosphatemia

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Presenting Signs/Symptoms

- ☐ Muscle cramps, fasciculations, tetany
- ☐ Tremor
- ☐ Headache, migraine, lumbalgia
- ☐ Nausea, vomiting, diarrhea
- ☐ Peripheral paresthesia
- ☐ Constipation, colic
- ☐ Hyperreflexia
- ☐ Asthenia, fatigue, tiredness
- ☐ Tachypnea
- ☐ CNS symptoms (e.g. mental status changes)
- ☐ Cardiac arrhythmia (atrial fibrillation, ventricular arrhythmia, extrasystoles)
- ☐ Other (please specify): _____

Medical History

- ☐ Hypocalcemia
- ☐ Pancreatitis
- ☐ Alcohol dependence
- ☐ Hypomagnesemia
- ☐ Thyroid Surgery
- ☐ Caffeine abuse
- ☐ Hypokalemia
- ☐ Chronic diarrhea
- ☐ Diabetes mellitus
- ☐ Hereditary hypomagnesemia
- ☐ Reduced Dietary Intake, diets
- ☐ Bone metastases
- ☐ TIA, ischemia stroke
- ☐ Vomiting
- ☐ Hypoparathyroidism
- ☐ Renal Disease (please specify): _____
- ☐ Chronic Bowel Disease (please specify): _____
- ☐ Other (specify): _____

Concomitant Meds/Substances (include prescription, OTC and herbal)

Eli Lilly and Company - Global Patient Safety **Case Number: .**

☐ Laxatives (please specify date/dose): _____

☐ Proton pump inhibitors (please specify): _____

☐ Bisphosphonates (please specify): _____

☐ Anticonvulsants (please specify): _____

☐ Other (please specify): _____

Laboratory Test	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Serum Calcium				
Serum Magnesium				
Serum Potassium				
Serum Parathormone				
Serum Phosphate				
Serum Albumin				
Arterial pH				
Ionized calcium				
Creatinine				
Glucose				
Vitamin D				
Creatinine kinase				
Cortisol				
TSH				
ECG abnormalities (please specify):				
Other: _____				
Other: _____				

Was this event related to a Lilly drug?

. _____ * ☐ Yes ☐ No ☐ Unknown

Event outcome

☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown

☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Form #2 Cancer/Neoplasm

Eli Lilly and Company - Global Patient Safety **Case Number: .**

Spontaneous Follow-up Form

Reported Events: .

Date: _____ **Lilly Case #:** . *

Information Provided By: _____ **Signature/Initials:** _____ **Fax:** Lilly (US) Global Patient Safety - (866) 644-1697 DC 4027

Patient's Name or Initials: . **Patient's Birth Date or Age:** .

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: _____

Lot/Control Number(if available): _____ Indication: _____

Dose: _____ Frequency: _____ Formulation: _____

Start Date: _____ Dose when event occured: _____ Route: _____

Drug D/C? ○ No ○ Yes Date D/C: _____ If Discontinued, did the event resolve? ○ Yes ○ No

Drug Restarted? ○ No ○ Yes Date Restarted: _____ If Restarted, did the event occur? ○ Yes ○ No

Cancer \ Neoplasm

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

☐ Please specify primary site: _____

☐ Neoplasm (benign mass/lesions) ☐ Possible malignant tumor - not yet confirmed

☐ Malignant tumor (please attach copy of pathology report or provide the information of Stage/Grade, Staging classification and tissue source):

Concomitant Medications/Substances (please include prescription, OTC and herbal)

Relevant Tests/Studies (please attach copy of pathology report if available)

Study	Result
Histopathology (please indicate stage/grade, staging classification and tissue source)	
Ultrasound	
CAT Scan	
MRI	
Other: _____	

Medical History/Risk Factors

Eli Lilly and Company - Global Patient Safety **Case Number: .**

☐ Chemotherapy:
☐ Estrogen use _____ years
☐ Diabetes mellitus
☐ Alcohol
☐ Immunosuppression: _____
☐ Other (please describe):

☐ Radiation therapy
☐ Tobacco use
☐ Obesity
☐ No known predisposing factors
☐ Environmental risk: _____

Treatment provided (please describe)

Was this event related to a Lilly drug?
. * ☐ Yes ☐ No ☐ Unknown

Event outcome
☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Not applicable