EU Risk Management Plan for TRAJENTA (linagliptin) and JENTADUETO (linagliptin+metformin)

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RMP version to be assessed as part of this application:	
RMP version number:	15.0
Data lock point for this RMP:	02 May 2024
Date of final sign off:	31 Jan 2025
Rationale for submitting an updated RMP:	To propose the removal of the remaining safety concerns from the RMP
Summary of significant changes in this RMP:	***Safety concerns*** *Important identified risk* Removal of pancreatitis (Modules SVII and SVIII and Parts V and VI) and pancreatitis questionnaire in Part VII Appendix 4 *Important potential risk* Removal of pancreatic cancer (Modules SVII and SVIII and Parts V and VI) and pancreatic cancer/malignancy questionnaire in Part VII Appendix 4 *Missing information* Removal of pregnancy/breastfeeding
Other RMP versions under evaluation:	Not applicable
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QPPV name:	Sven Kohler
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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PART I PRODUCT OVERVIEW

PI.Table 1 Product Overview

Active substances (INN or common name)	Linagliptin Linagliptin and metformin
Pharmacotherapeutic group (ATC code)	Trajenta: DPP-4 inhibitor (ATC code A10BH05) Jentadueto: DPP-4 inhibitor and biguanide (ATC code A10BD11)
Marketing Authorisation Holder	Boehringer Ingelheim International GmbH
Medicinal products to which this RMP refers	2
Invented names in the EEA	Trajenta Jentadueto
Marketing authorisation procedure	Centralised
Brief description of the products	*Chemical class* Trajenta: DPP-4 inhibitor Jentadueto: DPP-4 inhibitor and biguanide
	Summary of mode of action <u>Linagliptin</u> Linagliptin is a selective and reversible DPP-4 inhibitor. Inhibition of DPP-4 raises the level of incretin hormones (most importantly GLP-1), which are usually degraded rapidly by the enzyme. GLP-1 is secreted by the gut in response to a food stimulus and it stimulates insulin secretion by β-cells of the pancreas. Inhibiting DPP-4 therefore results in elevated GLP-1 levels with a more pronounced insulin secretion in response to food and thus improved glycaemic control in patients with T2DM. <u>Metformin</u> Although its mechanism of action is not yet fully understood, metformin lowers blood glucose levels primarily by suppressing hepatic gluconeogenesis. Metformin improves the insulin sensitivity of peripheral tissues, decreases gastrointestinal tract glucose absorption, and acts as an insulin sensitiser without exerting any direct effect on pancreatic β-cell insulin secretion.

	Important information about its composition Not applicable
Hyperlink to the Product Information	Product information
Indication in the EEA	*Current* **Trajenta:** Trajenta is indicated in adults with T2DM as an adjunct to diet and exercise to improve glycaemic control as: <u>monotherapy</u> • when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment. <u>combination therapy</u> • in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control. **Jentadueto** Jentadueto is indicated in adults with T2DM as an adjunct to diet and exercise to improve glycaemic control: • in patients inadequately controlled on their maximally tolerated dose of metformin alone • in combination with other medicinal products for the treatment of diabetes, including insulin, in patients inadequately controlled with metformin and these medicinal products • in patients already being treated with the combination of linagliptin and metformin as separate tablets.
	Proposed Not applicable

Dosage in the EEA	*Current* Trajenta 5 mg once daily Jentadueto: Linagliptin/metformin 2.5/850 mg and 2.5/1000 mg, both twice daily Outside the EEA 2.5/500 mg twice daily is available in addition
	Proposed Not applicable
Pharmaceutical form and strength	*Current* Trajenta and Jentadueto: Film-coated tablet
	Proposed Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
DPP-4	Dipeptidyl peptidase-4
EEA	European Economic Area
EU	European Union
GLP	Glucagon-like peptide
INN	International non-proprietary name
RMP	Risk Management Plan
T2DM	Type 2 diabetes mellitus

PART II SAFETY SPECIFICATION

MODULE SI EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATIONS

SI.1 TYPE 2 DIABETES MELLITUS

Note: Not all published epidemiology studies below distinguish between T1DM and T2DM due to inherent data source limitations; however, in the adult population T2DM constitutes the majority of cases.

SI.1.1 Incidence

The incidence estimates of T2DM increases with rising age in developed countries, and are slightly higher in men than in women. The variation in the incidence rates can be partially explained by variation in the lifestyle factors, economic status, and differences in age and ethnicity distributions in different countries.

A summary of the studies reporting incidence of T2DM in Europe from 1996 to 2010 is presented in the table below.

SI.Table 1 Incidence of T2DM reported in Europe from 1996 to 2010

Country	Time period	Sample size, n	Age, years	Method[2]	Incidence per 1000 PY			Reference
					Male	Female	Total	
UK	2010	-	All	READ	5.36	4.95	5.15	[R13-3433]
UK	1996-2005	1.8 mio	10-79	READ	4.9	3.7	4.2	[R10-2532]
Germany	1999-2008	2656	55-74	FPG	20.2[1]	11.3[1]	15.1	[R10-2532]
Italy	2000-2007	9 mio	≥30	ICD-9	-	-	4.0	[R12-3630]
Spain	1998-2005	1034	30-75	FPG	13.8[1]	9.0[1]	10.8[1]	[R12-1656]
Sweden	2003	230 750	>30	FPG, ICD-9	-	-	3.8	[R13-3431]

[1] Age-standardised (sex-standardised where appropriate)

[2] To minimise inclusion of T1DM patients and patients with other diabetes diagnoses, patients <18 years old were excluded, as were diagnoses codes for T1DM and gestational diabetes.

Certain ethnic groups seem to be at a higher risk of diabetes mellitus. A database study from the UK from 1993 to 2008 showed that the incidence of T2DM in 25 to 79-year-old individuals varied considerably by gender and ethnicity, see in the table below.

SI.Table 2 Incidence of T2DM per 1000 PY in 25 to 79-year-old persons in the UK (1993 to 2008), by sex and ethnicity

	Women				Men			
	Total N	T2DM incidence per 1000 PY			Total N	T2DM incidence per 1000 PY		
		Crude	Age-adjusted (95% CI)			Crude	Age-adjusted (95% CI)	
White/not recorded	1 240 470	4.2	4.1	(4.1-4.2)	1 220 355	5.3	5.3	(5.3-5.4)
Indian	6713	6.4	7.9	(6.7-9.1)	6544	8.6	9.6	(8.4-10.9)
Pakistani	4097	8.5	11.2	(9.2-13.2)	4707	9.9	13.2	(11.2-15.2)
Bangladeshi	1557	11.4	18.2	(12.9-23.5)	1876	12.8	19.3	(14.3-24.4)
Other Asian	4075	3.5	6.1	(2.7-9.4)	3322	7.1	8.1	(6.0-10.2)
Caribbean	6014	5.7	7.4	(6.3-8.4)	4416	7.0	7.0	(5.9-8.1)
Black African	9362	3.5	6.0	(4.5-7.4)	7695	5.4	8.8	(6.8-10.7)
Chinese	2619	3.4	5.4	(3.2-7.6)	1709	3.3	3.3	(1.9-4.8)
Other, including mixed	8228	3.6	5.9	(4.5-7.3)	6994	5.0	6.8	(5.5-8.2)

Data source: [R10-2049]

A 2016 study by Tamayo et al. used data from the DIMDI to estimate the prevalence and incidence of diabetes in Germany for 2009 and 2010 [R17-3431]. The incidence was estimated from differences in prevalence from one year to the next and the expected mortality of persons with and without diabetes. Since disease-specific mortality of individuals with and without diabetes was not available in Germany, estimates for the Danish population were used to create incidence estimates. 3 scenarios were used for estimating incidence: a) the ratio of mortality rates in Germany corresponding to rates in Denmark, or b) the incidence lies within a 15% range above, or c) the incidence lies below the values for Denmark. See table below.

SI.Table 3 Annual incidence of T2DM for male and female policyholders of German statutory health insurance funds (2009, 2010)

Mean age [years]	Incidence/1000 PY[1]
Male	
40-49	4
50-59	9
60-69	18
70-79	23-36
80-89	25-32
90-99	17-33
Female	
40-49	2
50-59	6
60-69	13
70-79	19-20
80-89	22-26
90-99	15-27

[1] Incidence estimates based on the Danish ratio of mortality risk (individuals with and without diabetes); R+15%. Mortality risk ratio 15% above respectively under the Danish estimates.

ICD-coded diagnosis data from the inpatient and outpatient sectors were used to define persons with diabetes.

Data source: [R17-3431]

SI.1.2 Prevalence

The estimates of the total diabetes prevalence in Europe in 2017, published in the IDF Diabetes Atlas, 8th Edition, show that the prevalence of diabetes mellitus varies worldwide. Age-adjusted comparative diabetes prevalence estimates (20-79 years) showed the highest prevalence reported in the North America and Caribbean (11.0%, 95% CI 9.2-12.5) followed by the Middle East and North Africa (10.8%, 95% CI 7.5-14.2), South and Central America (7.6, 95% CI 6.3-9.5), Western Pacific (8.6%, 95% CI, 7.6-11.0), South-East Asia (10.1%, 95% CI 7.9-12.8), Europe (6.8%, 95% CI 5.4-9.9), and Africa (4.4%, 95% CI 2.9-7.8). In most countries, T2DM has increased alongside rapid cultural and social changes: aging populations, increasing urbanisation, reduced physical activity, increased sugar consumption, and low fruit and vegetable intake. Much of the variation in the crude prevalence of DM worldwide is attributed to varying economic status, lifestyle factors, age distribution, and ethnicities in different countries [R18-1272]. The 57 countries and territories encompassing the IDF Europe Region include diverse populations, from Norway in the North, the Russian Federation in the East, Turkmenistan in the South and Greenland in the West. Similar to variation in the global crude prevalence estimates, there is wide variation in the Europe Region due to national income variation, lifestyle and ethnic differences and age distributions. While the Europe Region has the second lowest age-adjusted comparative

diabetes prevalence rate of any IDF region, there are several countries with relatively high diabetes prevalence rates. Turkey has the highest age-adjusted comparative prevalence (12.1% comparative prevalence) and the third-highest number of individuals with diabetes in the Europe Region (6.7 million, 95% CI 6.0-8.0) after Germany (7.5 million, 95% CI 6.1-8.3) and the Russian Federation (8.5, 95% CI 6.7-11.0).

The findings of individual studies that assessed prevalence of diabetes mellitus in Europe from 2000 to 2012 are presented in the table below, stratified by sex when available.

SI.Table 4 Crude prevalence of diabetes reported in Europe from 2000 to 2012

Country	Time period	Sample size [n]	Age, [years]	Method	Prevalence [%]			Reference
					Male	Female	Total	
UK	2011-12	5 mio	All	READ	-	-	3.3	[R15-1204]
	2005	1.8 mio	10 - 79	READ	4.8[1]	3.6[1]	3.9	[R11-5320]
Scotland	2011	5.2 mio	All	Various	-	-	4.7[1]	[R13-3430]
France	2006	10 038	≥18	Self-report	5.1	4.1	4.6	[R09-5903]
Germany	2009	21 262	≥18	Self-report	8.2[1]	9.3[1]	8.8[1]	[R12-4476]
	2009	65.6 mio[2]	20-79	ICD-10	8.31	6.69	6.9[3]	[R17-3431]
	2009	64.9 mio[2]	20-79	ICD-10	8.68	6.99	7.1[3]	[R17-3431]
Italy	2000	9 mio	≥30	ICD-9	-	-	3.0[1]	[R12-3630]
	2007	9 mio	≥30	ICD-9	-	-	4.2[1]	[R12-3630]
Denmark	2000	5.4 mio	All	ICD-10	2.7[1]	2.6[1]	2.7[1]	[R12-4477]
	2007	5.4 mio	All	ICD-10	4.3[1]	4.1[1]	4.2[1]	[R12-4477]
Sweden	2003	230 750	>30	FPG, ICD-9	-	-	3.5	[R13-3431]
Greece	2001-02	3042	≥20	FPG	7.8	6.0	6.9	[R10-2530]

[1] No differentiation between T1DM and T2DM.

[2] All ages (All policy holders of German statutory health insurance funds)

[3] Prevalence and corresponding intervals were calculated for the entire study sample of 2009 and 2010, respectively, and standardised according to age and sex for the German population (2007).

SI.1.3 Demographics of the population in the authorised indication and risk factors for the disease

Demographics

A description of patient characteristics with T2DM from a cross-sectional study including a total of 7597 patients from 8 European countries is presented in the following table. The mean age was 66.5 years and ranging from 64.2 years in the UK to 68.7 years in Belgium.

SI.Table 5 Multicentre study of T2DM in 8 European countries, March 2009 to December 2010

Country	All subjects (n)	Male gender (%)	Age, mean years ± SD
Belgium	1044	50.7	68.7 ± 10.6
France	1056	58.2	65.4 ± 11.1
Germany	959	48.5	67.7 ± 10.0
Ireland	950	59.8	64.6 ± 11.6
Italy	984	55.0	68.0 ± 9.4
The Netherlands	1021	55.7	66.2 ± 10.2
Sweden	550	60.2	67.7 ± 10.7
UK	1033	60.5	64.2 ± 11.9
Total	7597	55.8	66.5 ± 10.8

Data source: [R14-5420]

A description of patient characteristics with T2DM from a population-based study in Europe (UK, 2006 to 2007) is shown in the following table. Note that only patients aged 60 to 74 years at the time of the assessment were eligible for cohort entry.

SI.Table 6 Characteristics of T2DM patients enrolled in the Edinburgh Type 2 Diabetes Study, UK (Scotland), 2006 to 2007

	All subjects (n = 1057)	**Men (n = 544)**	**Women (n = 513)**
Age at assessment, years (SD)	67.9 (4.2)	68.1 (4.1)	67.7 (4.3)
Marital status			
Married	739 (70)	436 (80.4)	303 (59.1)
Living with a long-term partner	54 (5.1)	27 (5.0)	27 (5.3)
Single	156 (14.8)	33 (6.1)	123 (24.0)
Widowed	106 (10.0)	46 (8.5)	60 (11.7)
Education			
University/college	170 (16.1)	99 (18.2)	71 (13.8)
Other professional/technical	303 (28.7)	157 (28.9)	146 (28.5)
Secondary school	577 (54.6)	283 (52.0)	294 (57.3)
Primary school	7 (0.7)	5 (0.9)	2 (0.4)
Employment status			
Worker	152 (14.4)	106 (19.5)	46 (9.0)
Retired	855 (80.9)	413 (75.9)	442 (86.2)
Other (housewife, unemployed)	50 (4.7)	31 (5.7)	19 (3.7)
Ethnic group			
White	1007 (95.3)	513 (94.3)	494 (96.3)
Other	50 (4.7)	31 (5.7)	19 (3.7)
Smoking	146 (13.8)	85 (15.6)	61 (11.9)
Alcohol consumption			
Never	213 (20.3)	63 (11.6)	150 (29.5)
1-4 drinks per month	459 (43.7)	207 (38.3)	252 (49.5)
2-5 drinks per week	268 (25.5)	186 (34.4)	82 (16.1)
≥6 drinks per week	110 (10.5)	85 (15.7)	25 (4.9)
Weight, kg (SD)	86.4 (16.2)	90.3 (15.4)	82.4 (15.9)
BMI, kg/m^2 (SD)	31.4 (5.7)	30.3 (4.9)	32.6 (6.2)
Waist circumference, cm (SD)	106.9 (12.8)	108.2 (12.1)	105.5 (13.5)
Duration of diabetes mellitus, years (SD)	9.1 (6.5)	9.4 (6.6)	8.7 (6.3)
Treatment of diabetes			
Diet alone	200 (18.9)	101 (18.6)	99 (19.3)
Hypoglycaemic oral agents	673 (63.7)	353 (64.9)	320 (62.4)
Insulin ± hypoglycaemic oral agents	184 (17.4)	90 (16.5)	94 (18.3)

Categorical data are presented as n (%), continuous variables as means (SD).
Data source: [R13-1769]

The South London Diabetes Cohort (UK, 2008 to 2011) recruited 1506 newly diagnosed patients with T2DM (mean age 55.6±11.07 years, 55% men). The distribution of patients according to ethnicity was 51% White, 38% Black, and 11% South Asian/other, respectively; White patients were significantly older, with a higher proportion of male patients [R13-1754].

Risk factors
According to the consensus statement on T2DM prevention, issued in 2007 by the IDF [R07-1222] and the 2014 ADA statement "Standards of Medical Care in Diabetes" [R14-0344], the modifiable risk factors for T2DM development are as follows:

- Overweight and obesity (central and total)
- Sedentary lifestyle
- Previously identified glucose intolerance (IGT and/or IFG)
- Metabolic syndrome: hypertension, decreased HDL cholesterol, increased triglycerides
- Dietary factors: high total calorie and low dietary fibre intake, a high glycaemic load and a low polyunsaturated to saturated fat ratio are potential predisposing factors
- Intrauterine environment
- Inflammation

The following are non-modifiable factors for T2DM [R07-1222, R14-0344]:

- Age
- Gender
- Ethnicity (people of African American, Hispanic/Latino, Native American, Asian American, South Asian or Pacific Islander ethnicity are at high risk)
- Family history of T2DM
- Prior gestational diabetes or delivery of a baby weighing >9 lbs (approximately 4 kg)
- Polycystic ovary syndrome
- History of CV disease
- Acanthosis nigricans

Additionally, particular gene variants, such as the TCF7L2 and, potentially, other loci have been found to confer additional risk for T2DM [R12-5231].

SI.1.4 The main existing treatment options

The following agents are currently approved in various countries for the treatment of T2DM:

Biguanides
The most important member of this class is metformin, favoured as a first-line agent by most existing clinical guidelines. Metformin works primarily by reducing liver release of blood glucose from glycogen stores and secondarily, by provoking some increase in cellular uptake of glucose in body tissues. Metformin is associated with lower risk for hypoglycaemia as opposed to insulin or SUs [R12-1081].

Sulphonylureas
Prominent members of this group are glibenclamide and gliclazide. SUs are often found in treatment protocols to reach and maintain glycaemic control. SUs increase glucose-stimulated insulin secretion by the pancreas and, thereby, lower blood glucose even in the face of insulin resistance. SUs are associated with an increased risk of hypoglycaemia, compared to other oral anti-diabetic drugs [R12-1081].

Thiazolidinediones
The TZDs or 'glitazones' are a class of oral antidiabetic drugs that improve metabolic control in patients with type 2 diabetes through the improvement of insulin sensitivity. TZDs exert their antidiabetic effects through a mechanism that involves activation of PPAR gamma, a nuclear receptor. TZD-induced activation of PPAR gamma alters the transcription of several genes involved in glucose and lipid metabolism and energy balance, including those that code for lipoprotein lipase, fatty acid transporter protein, adipocyte fatty acid binding protein, fatty acyl-CoA synthase, malic enzyme, glucokinase and the GLUT4 glucose transporter [R19-0054]. TZDs are associated with lower risk for hypoglycaemia as opposed to insulin or SUs, but possibly with oedema and heart failure [R12-1081].

Meglitinides
Meglitinides (nateglinide, repaglinide, and their analogues) quickly stimulate insulin release; they can be taken with food, unlike SUs that must be taken prior to food (sometimes some hours before, depending on the drug).

Insulin therapy
For patients with T1DM, it is a necessary life-long life-saving treatment. In T2DM, many traditional treatments are not successful in helping patients maintain their blood glucose targets. Glycaemic control often deteriorates over time, resulting in the necessity to start insulin therapy.

DPP-4 inhibitors
DPP-4 inhibitors or gliptins (e.g. saxagliptin, sitagliptin, linagliptin, alogliptin) are a class of oral hypoglycaemics that block DPP-4. They are used to treat T2DM. The mechanism of DPP-4 inhibitors is to increase incretin levels (GLP-1 and GIP), which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels.

Injectable GLP-1 mimetics
The GLP-1 analogues (e.g. exenatide, liraglutide) increase insulin output from the β-cells among other effects. Recent findings from the LEADER study, a randomized, double blind, placebo-controlled cardiovascular outcome study of the GLP-1 agonist, liraglutide, showed significant reduction in all-cause and CV mortality. These findings suggest that the GLP-1 agonist class of drugs may also provide CV benefits in high-risk patients with type 2 diabetes [P17-03447].

SGLT-2 inhibitors
SGLT-2 plays a major role in physiology of glucose reabsorption from proximal part of kidney. Almost all glucose excreted through glomerular filtration is reabsorbed via SGLT-2 until blood glucose level reaches the renal threshold for glucose, i.e. 180 mg/dL. SGLT-2 inhibition (e.g. by dapagliflozin, canagliflozin, empagliflozin) lowers this threshold thereby causing urinary glucose excretion and results in insulin-independent reduction of plasma glucose levels with low risk of hypoglycaemia, negative energy balance with weight reduction, and potential blood pressure reduction. In the EMPA-REG Outcome trial (1245.25), empagliflozin demonstrated significant benefit in patients with type 2 diabetes with established cardiovascular disease by reducing mortality mostly due to CV death and hospitalisation for heart failure.

Alpha-glucosidase inhibitors
Alpha-glucosidase inhibitors (e.g. acarbose) prevent the degradation of starch and other complex carbohydrates into glucose.

Bile acid sequestrants
Bile acid sequestrants (e.g. colesevelam) bind to and prevent reabsorption of bile acid, thereby depleting systemic cholesterol. The mechanism by which they improve glycaemic control is not fully understood, but colesevelam is currently approved in the US for management of hyperglycaemia in patients with T2DM.

Dopamine receptor agonists
Only bromocriptine is used in the treatment of T2DM. The mechanism by which bromocriptine improves glycaemic control is unknown, but it is currently approved in the US for management of hyperglycaemia in patients with T2DM.

Non-pharmacological treatment options
Diet and lifestyle interventions are recommended immediately after diagnosis by most existing clinical guidelines, with weight loss as the main focus. The 2017 ADA statement "Standards of Medical Care in Diabetes" recommends "individualised medical nutrition treatment as needed to achieve treatment goals". The daily intake of alcohol should be limited to a moderate amount (1 drink per day or less for adult women and 2 drinks per day or less for adult men). The guideline references the US Department of Health and Human Services' physical guidelines suggesting that adults over age 18 years engage in at least 150 min per week of moderate-intensity physical activity (50% to 70% of maximum heart rate), or 75 min per week of vigorous-intensity, or an equivalent combination of the two, spread over at least 3 days per week with no more than 2 consecutive days without exercise [R17-0809].

Several guidelines recommend bariatric surgery for T2DM patients with a BMI >35 kg/m^2 especially if the diabetes or associated co-morbidities are difficult to control with lifestyle and pharmacologic therapy [R17-0809, P10-00533]. However, most guidelines agree that there is insufficient evidence to recommend surgical treatment options for patients with T2DM and with a BMI ≤35 kg/m^2.

SI.1.5 Natural history of the indicated condition in the population, including mortality and morbidity

T2DM is a progressive disease in which the risk of myocardial infarction, stroke, microvascular events, are strongly associated with hyperglycaemia.

Tancredi et al (2015) [R17-3434] investigated excess mortality among individuals with T2DM in Sweden. Patients with at least one entry in the National Diabetes Register from 01 Jan 1998 until 31 Dec 2011 were included in the study. In Cox regression analyses, the adjusted HR was 1.15 (95% CI 1.14-1.16). The cardiovascular mortality rate per 1000 PY was 17.2 among patients with T2DM, as compared with 12.7 among controls. The adjusted HR was 1.14 (95% CI 1.13-1.15).As compared with controls, the HR for death from any cause among patients younger than 55 years of age and with an HbA_{1c} <6.9% was 1.92 (95% CI, 1.75-2.11). Among patients with normoalbuminuria, the HR for death among those <55 years with an HbA_{1c} < .9%, as compared with controls, was 1.60 (95% CI 1.40-1.82).

A study in the UK CPRD (2004 to 2010) followed 87 098 patients with T2DM aged 40 to 65 years at baseline, and 65 300 non-diabetes controls matched on age, sex and general practice. People with T2DM have twice the risk of dying from any cause and 3 times the risk of CV death compared with people without diabetes [R14-5417].

Another study in the UK (2000 to 2010) identified 57 946 patients with T2DM (mean age at baseline 65.7, 55.4% men) in the THIN database and followed them over a mean of 6.76 years. All-cause mortality rate in this population was 43.65 per 1000 PY [R15-4246].

The mortality rates for diabetes mellitus, provided in 2009 by the Organization for Economic Co-operation and Development, are given in the table below for selected countries.

SI.Table 7 Total diabetes mellitus (no differentiation between type 1 and type 2) deaths per 100 000 population (age-standardised) in various countries in 2005

Diabetes mellitus	Standardised death rates in 2005 per 100 000 population				
	Germany	France	UK	US	Japan
Total	16.2	10.9	6.7	20.3	5.7
Men	17.6	13.8	7.9	23.6	7.4
Women	14.5	8.6	5.8	17.6	4.1

Data source: [R13-2549]

A study in Tayside (Scotland, UK, 1993 to 2004) identified 10 532 individuals newly diagnosed with T2DM during the study period and followed them for up to 12 years for mortality [R13-0708]. All-cause mortality in T2DM patients, as well as matched non-diabetic controls, by sex and age group, is presented in the table below.

SI.Table 8 Death rates from all causes in patients with T2DM and in those without diabetes mellitus in Tayside, Scotland (1993 to 2004), by sex and age

Age group [years]	T2DM		No diabetes[1]		Excess death rate per 1000 PY
	Total (n deaths)	Death rate per 1000 PY (95% CI)	Total (n deaths)	Death rate per 1000 PY (95% CI)	
Men					
35–44	419 (11)	5.60 (2.29–8.90)	836 (5)	1.25 (0.15–2.35)	4.4
45–54	1052 (62)	12.84 (9.65–16.04)	2105 (61)	6.13 (4.59–7.67)	6.7
55–64	1557 (198)	28.61 (24.62–32.59)	3118 (271)	18.87 (16.62–21.11)	9.7
65–74	1594 (371)	56.53 (50.78–62.29)	3178 (595)	43.38 (39.90–46.87)	13.2
≥75	884 (341)	113.68 (101.61–125.74)	1774 (646)	104.80 (96.72–112.88)	8.9
All	5506 (983)	42.23 (39.59–44.87)	11 011 (1578)	32.75 (31.13–34.36)	9.5
Women					
35–44	328 (10)	6.40 (2.43–10.36)	638 (4)	1.31 (0.03–2.60)	5.1
45–54	749 (38)	11.24 (7.67–14.82)	1512 (24)	3.36 (2.01–4.70)	7.9
55–64	1233 (123)	20.85 (17.17–24.54)	2452 (149)	12.37 (10.38–14.35)	8.5
65–74	1506 (255)	40.55 (35.58–45.53)	3032 (408)	30.81 (27.82–33.80)	9.7
≥75	1210 (454)	113.92 (103.44–124.40)	2411 (799)	91.14 (84.82–97.46)	22.8
All	5026 (880)	41.68 (38.92–44.43)	10 045 (1384)	31.27 (29.63–32.92)	10.4

[1] Matched by sex, age and deprivation
Data source: [R13-0708]

SI.1.6 Important co-morbidities

In patients with T2DM, a cluster of diseases and medical conditions is often found. Below is a list (non-comprehensive) of important co-morbidities experienced by individuals with T2DM:

- Hypertension
- Obesity
- Dyslipidaemia
- Metabolic syndrome
- Cardiovascular disease

  - Coronary heart disease
  - Cardiac failure
  - Myocardial infarction
  - Peripheral arterial disease
- Retinopathy and macular oedema
- Cerebrovascular disease (stroke)
- Neuropathy
- Nephropathy
- Liver injury
- Kidney injury/disease (CKD, ESRD, acute kidney failure)
- Malignancies
- Pancreatitis
- Fractures
- Infections
- Cognitive impairment

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SI.2.2 Unpublished references

Not applicable.

ABBREVIATIONS

ADA	American Diabetes Association
BMI	Body mass index
CI	Confidence interval
CKD	Chronic kidney disease
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
DIMDI	Deutsche Institut für Medizinische Dokumentation und Information
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase-4
ESRD	End-stage renal disease
FPG	Fasting plasma glucose
GIP	Gastric inhibitory polypeptide
GLP-1	Glucagon-like peptide-1
GLUT4	Glucose transporter type 4
HbA_{1c}	Glycated haemoglobin

HDL	High density lipoprotein
HR	Hazard ratio
ICD	International Classification of Diseases
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
PPAR	Peroxisome proliferator-activated receptor
PY	Patient years
READ	Standard clinical terminology system used in general practice in the UK
SD	Standard deviation
SGLT-2	Sodium-dependent glucose co-transporter 2
SU	Sulphonylurea
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TCF7L2	Transcription factor 7 like 2
THIN	The Health Improvement Network (database)
TZD	Thiazolidinedione
UK	United Kingdom
US	United States

MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE

SII.1.1 Toxicity

Linagliptin

The toxic potential of linagliptin has been explored in an extensive non-clinical safety programme including studies using the intended oral route of human administration as well as supporting studies using the intravenous route. In addition, genotoxicity studies were performed both *in vivo* and *in vitro*. Linagliptin was administered up to maximum dose levels allowing the identification of toxicological target organs to mouse, rat, rabbit, dog, and cynomolgus monkey (Macaca fascicularis). All pivotal studies were conducted according to GLP regulations and the respective international guidelines at the time of conduct.

Linagliptin was well tolerated in all investigated species. Side effects were only seen at doses with a high safety margin to clinical use (for the safety factors the following assumptions were used: 5 mg as the MRHD associated with clinical exposure at steady state of $AUC_{0\text{-}24h}$ = 158 nM h and C_{max} = 11.1 nM).

The acute toxicity of linagliptin was low as indicated by an approximate lethal dose of 1000 to 2000 mg/kg evaluated in rodents [U05-1899, U05-1901, U05-1902, U05-1903]. The low acute toxicity applies accordingly for non-rodents. No specific acute toxicity studies were performed, but repeat-dose studies showed that doses up to 300 mg/kg did not cause mortality in the cynomolgus monkey [U08-2215-01] (corresponding to >1000-fold clinical exposure at MRHD for both peak plasma levels and AUC).

Pseudo-allergy seen in dogs [U05-1944] at peak plasma levels 450-fold above the clinical relevant levels were shown not to occur in non-human primates up to very high doses and peak plasma levels (>3000-fold). Healthy volunteers did not show this effect even at plasma levels inducing pseudo-allergy in dogs, indicating that this effect is of no relevance for humans.

The oral repeat-dose toxicity of linagliptin was evaluated in mice for up to 3 months, in rats for up to 6 months, in dogs for up to 4 weeks, and in cynomolgus monkeys for up to 12 months. Signs of toxicity (target organs such as liver, kidneys, gastrointestinal tract, reproductive organs, lungs, and the lymphoid organs) were observed at doses far in excess of those recommended for therapy (in the following indicated as multiples of clinical exposure at the MRHD based on AUC). In the 6-month rat study [U07-1910], the NOAEL was 30 mg/kg/day (66-fold MRHD). In the 12-month toxicity study in cynomolgus monkeys [U08-1185-01], a NOAEL of 10 mg/kg/day was derived (40-fold MRHD). The results of the performed non-clinical studies did not indicate a risk of nephrotoxicity or hepatotoxicity for patients at the recommended human dose.

The main metabolite CD 1790 were present in all investigated species and wide safety margins (28- and 92-fold to human exposure in rat and cynomolgus monkey respectively) were shown with regard to human exposure.

Necrotic skin lesions, observed after administration of other DPP-4 inhibitors, were not seen in any of the performed preclinical studies including cynomolgus monkey studies up to one year [U08-1185-01] with a high dose level of 100 mg/kg/day corresponding to 791-fold MRHD. There was no evidence for dermal intolerance, and skin sensitisation.

All repeat-dose toxicity studies performed with linagliptin revealed consistently no evidence for pancreatitis or any other adverse effect on the exocrine pancreas.

The results of the *in vitro* and *in vivo* mutagenicity studies showed that linagliptin and the main metabolite CD 1790 are free of any genotoxic potential [U04-1756, U04-1827, U04-1847, U06-1188, U06-1585, U07-2080].

The results of the reproduction and developmental toxicity studies indicated wide safety margins to clinical use. No effect on mating, fertility and bearing live young was observed in rats [U06-2047] up to and including the highest tested dose of 240 mg/kg/day (943-fold MRHD). There was no evidence of teratogenicity at dosages up to 240 mg/kg/day (943-fold MRHD) in the rat [U06-2047], and up to 150 mg/kg/day (1943-fold MRHD) in the rabbit [U06-1200]. A NOAEL of 30 mg/kg/day (49-fold MRHD) and 25 mg/kg (78-fold MRHD) was derived for embryofoetal toxicity in the rat and the rabbit, respectively. In the pre- and postnatal development study in rats [U07-1558] linagliptin produced maternal toxicity at 300 mg/kg/day (1506-fold MRHD). The offspring's fertility, however, was not changed. The NOAEL for both maternal and offspring toxicity was 30 mg/kg/day (49-fold MRHD). Linagliptin crosses the blood-placenta barrier and distributes into the embryo and fetus [U10-1332-01]. Moreover, linagliptin is excreted with milk as investigated in rats [U08-1929-01].

The carcinogenic potential of linagliptin was assessed in 2-year studies in mice and rats. No evidence of a carcinogenic potential was seen up to and including the high dose groups of 80 mg/kg/day (242-fold MRHD) in the mouse [U10-1500-01] and 60 mg/kg/day (418-fold MRHD) in the rat [U10-1502-01].

Linagliptin/metformin

There were no toxicological findings indicating a safety concern which were caused by the combination of linagliptin and metformin. No new target organs or an exacerbated toxicity of the linagliptin/metformin combination were identified. The only observed interaction between linagliptin and metformin in non-clinical safety studies was a reduction of body weight gain. This effect is considered not adverse but rather an additive pharmacodynamic effect of the 2 antidiabetic compounds.

In the 3-month combination toxicity study in the rat, a NOAEL for linagliptin/metformin of 0.5/100 mg/kg/day (1.0x MRHD for linagliptin, 1.4x MRHD for metformin) was derived based on metformin related findings. All adverse findings in the combination studies were attributed to metformin at dosages of 400 mg/kg/day (7.4x MRHD) or higher [U10-1492].

There was also no indication of a teratogenic effect attributable to the co-administration of linagliptin and metformin [U10-2448].

SII.1.1.1 Relevance to human usage

Linagliptin
Toxicity data did not indicate safety concerns for healthy subjects or patients, which would preclude clinical development or would not be assessable by routine safety laboratory or regular pharmacovigilance activities. Signs of toxicity were only observed at doses far in excess of those recommended for therapy. Relating to the results of non-clinical studies (see below), all potential clinical relevant safety concerns were addressed and followed up in clinical studies.

The performed toxicity studies revealed no toxicity of clinical relevance.

Linagliptin/metformin
The performed toxicity studies revealed no new or exacerbated toxicity of clinical relevance with the linagliptin/metformin combination.

SII.1.2 Safety pharmacology

Linagliptin
Core battery studies were conducted according to ICH guidance documents ICH S7A and ICH S7B.

Potential effects on the CNS were investigated in rats after single oral administration of 6 mg/kg, 60 mg/kg, or 600 mg/kg linagliptin [U05-1935]. In this modified Irwin study, no marked or consistent behavioural or physiological changes were seen. In addition, no significant effects on body temperature or spontaneous locomotory activity were observed.

A comprehensive cardiovascular profiling was performed both *in vitro* and *in vivo*. Linagliptin had no effect on hERG-mediated potassium current in concentrations up to 10 µM [U04-1088]. In guinea pig papillary muscles exposed to concentrations up to 10 µM, resting membrane potential, action potential amplitude and overshoot, and maximal upstroke velocity were not affected. There was a concentration-dependent shortening of the action potential, beginning at 0.3 µM that increased up to a 7% shortening (of action potential duration 90) at 10 µM. In conclusion, these in vitro studies suggest, that linagliptin has a low proarrhythmic potential for delayed ventricular repolarisation. Clinical data, provided by the thorough QT study, indicate that the observed in vitro effect was of no clinical relevance (study 1218.32) [U09-1067-01] in healthy male volunteers.

Potential *in vivo* effects of linagliptin on the CV system were studied in the telemetered cynomolgus monkey at dosages of 12, 60, and 150 mg/kg. High plasma concentrations of up to 18 900 nM (1702-fold clinical C_{max}) were reached at a dose of 150 mg/kg. There was no relevant treatment related changes in the ECG (lead II) at doses up to 150 mg/kg [U06-1700]. CV investigations were also conducted in repeated-dose toxicity studies. In the 4-week toxicity study in beagle dogs doses up to 9 mg/kg/day (210-fold clinical C_{max}) were free from

any relevant effect of linagliptin on blood pressure, heart rate and ECG. Changes in haemodynamic parameters (hypotension, tachycardia) seen at 45 mg/kg/day (955-fold clinical C_{max}) were considered to be pseudo-allergy related [U05-1944]. In cynomolgus monkeys, showing no pseudo-allergy, no treatment-related changes were detected in the ECG and blood pressure measurements in the toxicity studies up to 12 months duration and at dosages up to 300 mg/kg/day (2523-fold clinical C_{max}) [U05-2481, U07-1072, U08-1185-01]. In conclusion, the preclinical safety data did not appear to indicate high potential for linagliptin-related CV risk.

Effects on respiratory function were tested in rats given a single oral dosage of 0, 6, 60, or 600 mg/kg linagliptin [U05-1967]. Oral dosages of 6 or 60 mg/kg produced no effect on respiratory rate, tidal volume, and minute volume. At a dosage of 600 mg/kg, a statistically significant increase in tidal volume and a significant decrease in respiration rate and minute volume at 30 min post-dose were seen. A dose 600 mg/kg was associated with plasma levels of 3099-fold clinical C_{max} [U05-1937].

In conclusion, the safety pharmacology assessment of CNS, CV, and respiratory effects did not identify any significant liabilities of linagliptin.

Linagliptin/metformin
No specific safety pharmacology studies with the linagliptin/metformin combination have been performed at BI according to the EU guideline on the non-clinical development of medicinal products (EMEA/CHMP/SWP258498/2005) and according to ICH M3(R2).

SII.1.2.1 Relevance to human usage

The performed toxicity studies revealed no adverse findings of clinical relevance.

SII.1.3 Other toxicity-related information or data

'Other toxicity-related information or data' were assessed for linagliptin monotherapy included malignancies (see below). No additional non-clinical data for linagliptin/metformin will be obtained. No additional aspects based on the metformin component of the fixed dose combination are to be covered.

Available data suggest no new or exacerbated toxicity of clinical relevance with the linagliptin/metformin combination.

SII.1.3.1 Malignancies

Exenatide, liraglutide, and DPP-4 inhibitors increased beta-cell proliferation in animal studies, and in one small study of a transgenic rodent model, the DPP-4 inhibitor sitagliptin was demonstrated to increase pancreatic ductal hyperplasia [R10-5403]. However, these limited animal studies do not provide relevant experimental data that indicate a carcinogenic potential of DPP-4 inhibitors.

Based on the publicly available data of the 2-year carcinogenicity studies performed with the marketed DPP-4 inhibitors sitagliptin, vildagliptin, and saxagliptin there is also no indication of a carcinogenic potential that is associated with DPP-4 inhibition.

The "gold standard" for determining potential carcinogenic activity of a drug is 2-year carcinogenicity studies in rodents. Results of the performed studies indicate that there was no evidence for a carcinogenic potential of linagliptin. This included the high dose groups of 80 mg/kg/day (242-fold higher than the clinical exposure, based on the AUC) in the mouse [U10-1500-01] and 60 mg/kg/day (418-fold higher than the clinical exposure, based on the AUC) in the rat [U10-1502-01]. Based on the data of the 2-year carcinogenicity studies in rats and mice there is no indication of a carcinogenic potential of linagliptin.

SII.1.3.1.1 Relevance to human usage

The performed non-clinical studies with linagliptin revealed no carcinogenic potential of linagliptin.

SII.1.4 Special populations: paediatrics

The animal models used in the non-clinical development of linagliptin are considered to sufficiently cover the stage of development in the intended paediatric population (10 to 17 years of age). Adverse effects after administration of linagliptin in laboratory animals were only observed at dosage levels with a very high safety margin to clinical use.

There was no requirement for a dedicated non-clinical study (e.g. in juvenile animals) prior to initiating studies in paediatric patients and BI has not and does not intend to conduct one.

Linagliptin/metformin received a product specific waiver for paediatric studies (EMA/PDCO/802450/2009; EMA-000699-PIP01-09). Therefore, no specific studies in juvenile animals will be performed.

SII.1.5 Special populations: patients with severe renal impairment, severe hepatic impairment, and elderly patients (>80 years)

The available non-clinical data do not indicate any risk associated with use of the linagliptin/metformin combination to renal or hepatic function [U10-1492]. Metformin is contraindicated in patients with severe renal or severe hepatic impairment [R15-1201]. Because of the metformin component of the fixed dose combination, linagliptin/metformin is contraindicated in patients with severe renal or severe hepatic impairment. Data of the individual compounds do not indicate an increased risk for elderly patients (>80 years) [U07-1910, U08-1185-01, R10-5239]. No non-clinical studies regarding this endpoint for the linagliptin/metformin combination were performed.

SII.2 REFERENCES

SII.2.1 Published references

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SII.2.2 Unpublished references

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U04-1827 BI 1356 BS: Mutagenicity study for chromosomal aberrations in human lymphocytes in vitro. 04B069. 11 Oct 2004

U04-1847 BI 1356 BS: Mutagenicity study using the micronucleus assay in rat bone marrow (Part of the 4-week oral (gavage) toxicity study, Study No. 04B042). 04B067. 11 Oct 2004

U05-1899 BI 1356 BS: Single oral (gavage) dose toxicity in mice. 04B115. 13 Jul 2005

U05-1901 BI 1356 BS: Single oral (gavage) dose toxicity study in rats. 04B114. 13 Jul 2005

U05-1902 BI 1356 BS: Supplementary single oral (gavage) dose toxicity study in mice. 04B170. 26 Jul 2005

U05-1903	BI 1356 BS: Supplementary single oral (gavage) dose toxicity study in rats. 04B169. 26 Jul 2005
U05-1935	BI 1365 BS modified Irwin study in male rats including body temperature and locomotor assessment (single oral administration). BOI 285/042907 07 Mar 2005
U05-1937	BI 1356 BS: 4-week oral (gavage) toxicity study in rats. 04B042. 01 Aug 2005
U05-1944	BI 1356 BS: 4-week oral (gavage) toxicity study in beagle dogs with a 4-week recovery period. 04B060. 05 Aug 2005
U05-1967	BI 1356 BS: Evaluation of respiratory parameters in the conscious male rat using whole body bias flow phletysmography (single dose administration). BOI 286/042899. 21 Oct 2004
U05-2481	BI 1356 BS: Toxicity study by oral gavage administration to cynomolgus monkeys for 4 weeks followed by a 4 week recovery period. BOI 309/043369. 16 Sep 2005
U06-1188	CD 1750 XX (metabolite of BI 1356 BS): Mutagenicity study using the S. typhimurium/mammalian microsome assay (Ames test). 05B282. 04 Apr 2006
U06-1200	BI 1356 BS: Study for effects on embryo-fetal development in rabbits by oral (gavage) administration. 05B097. 08 May 2006
U06-1585	CD 1750 (metabolite of BI 1356): Mutagenicity study for chromosomal aberrations in human lymphocytes in vitro. 05B283. 10 Jul 2006
U06-1700	BI 1356 BS: Telemetric evaluation of cardiovascular effects in conscious cynomolgus monkeys. BOI 311/052279. 14 Jun 2006
U06-2047	BI 1356 BS: Study of fertility and early developement to implantations in rats by oral administration, gavage. 05B189. 05 Dec 2006
U07-1072	BI 1356 BS: Toxicity Study by Oral Gavage Administration to Cynomolgus Monkeys for 13 Weeks Followed by a 6 Week Recovery Period. BOI 315/052597. 10 May 2007
U07-1558	BI 1356 BS: Study for effects on preand postnatal development including maternal function in rats by oral administration. BI internal report 05B241, 14 Feb 2008
U07-1910	BI 1356 BS: 26-week oral (gavage) toxicity study in rats. BI Internal number 05B285, 06 Feb2008.

U07-2080	CD 1750 XX (metabolite of BI 1356 BS): Mutagenicity study using the S. typhimurium/mammalian microsome assay (Ames test) - Supplementary study. 07B046. 15 Nov 2007
U08-1185-01	BI 1356 BS Toxicity Study by Oral Gavage Administration to Cynomolgus Monkeys for 52 Weeks Followed by an 8 Week Recovery Period. BOI 0331/072859. 21 Feb 2008
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U09-1067-01	Assessment of the effect of 5 mg and 100 mg of BI 1356 as single dose on the QT interval in healthy female and male subjects. A randomised, placebo controlled, double-blind, four-way crossover study with moxifloxacin as positive control. 1218.32. 27 Jan 2009
U10-1332-01	Determination of maternal and embryo-fetal exposure to BI 1356 BS after repeated oral dosing of BI 1356 BS to pregnant rats. 09B138, B3941. 23 Feb 2010
U10-1492	BI 1356 BS (linagliptin) and Metformin: 13-week oral (gavage) combination toxicity study in rats. 09B104. 12 Oct 2010
U10-1500-01	BI 1356 BS Carcinogenicity Study by Oral Gavage Administration to CD-1 Mice for 104 Weeks (BOI0330). 08 Mar 2010
U10-1502-01	BI 1356 BS: Carcinogenicity Study by Oral Gavage Administration to Han Wistar rats for 104 Weeks. (BOI0332). 09 Mar 2010
U10-2448	BI 1356 (Linagliptin) and Metformin: Study for effects on embryo-fetal development in rats by oral (gavage) administration. 09B138. 26 Oct 2010

ABBREVIATIONS

3T3 NRU-PT	Neutral red uptake phototoxicity assay
AUC	Area under the curve
BI	Boehringer Ingelheim
CHMP	Committee for Human Medicinal Products
Cmax	Maximum concentration
CNS	Central nervous system
CV	Cardiovascular
DDI	Drug-drug interaction
DPP-4	Dipeptidyl peptidase 4
ECG	Electrocardiogram
EU	European Union
GLP	Good laboratory practice
hERG	Human Ether-a-go-go Related Gene
ICH	International Conference on Harmonization
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
MRHD	Maximum recommended human dose
NOAEL	No observed adverse effect level
SWP	Safety Working Party
TGF	Tumour growth factor
TNF	Tumour necrosis factor

MODULE SIII CLINICAL TRIAL EXPOSURE

An overview of the safety analysis sets used for the exposure calculations is given in the following table.

SIII.Table 1 Overview on analysis sets

Description	Analysis set	Trials included
Pooled clinical trials		
Randomised, double-blind, placebo-controlled studies with linagliptin 5 mg in patients with T2DM	SAF-2	1218.2, 1218.3, 1218.5, 1218.6, 1218.15, 1218.16, 1218.17, 1218.18, 1218.23, 1218.35, 1218.36, 1218.37, 1218.43, 1218.46, 1218.50, 1218.52, 1218.61, 1218.62, 1218.63, 1218.64, 1218.65, 1218.66, 1218.75, 1218.89, 1218.105, 1218.149, 1264.3, 1275.1, 1275.10, 1275.13, and 1288.18
Randomised, double-blind, placebo-controlled trials comparing linagliptin + metformin to placebo + metformin in patients with T2DM	SEA-2	1218.6, 1218.17, 1218.46, 1218.52, 1218.62, 1218.65, 1218.105, 1288.18
Randomised, double-blind Phase 3 trials		
A multicentre, international, randomised, parallel group, double-blind, placebo-controlled, CV safety and renal microvascular outcome study with linagliptin, 5 mg once daily in patients with T2DM at high vascular risk.	NA	1218.22
A multicentre, international, randomised, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk.	NA	1218.74

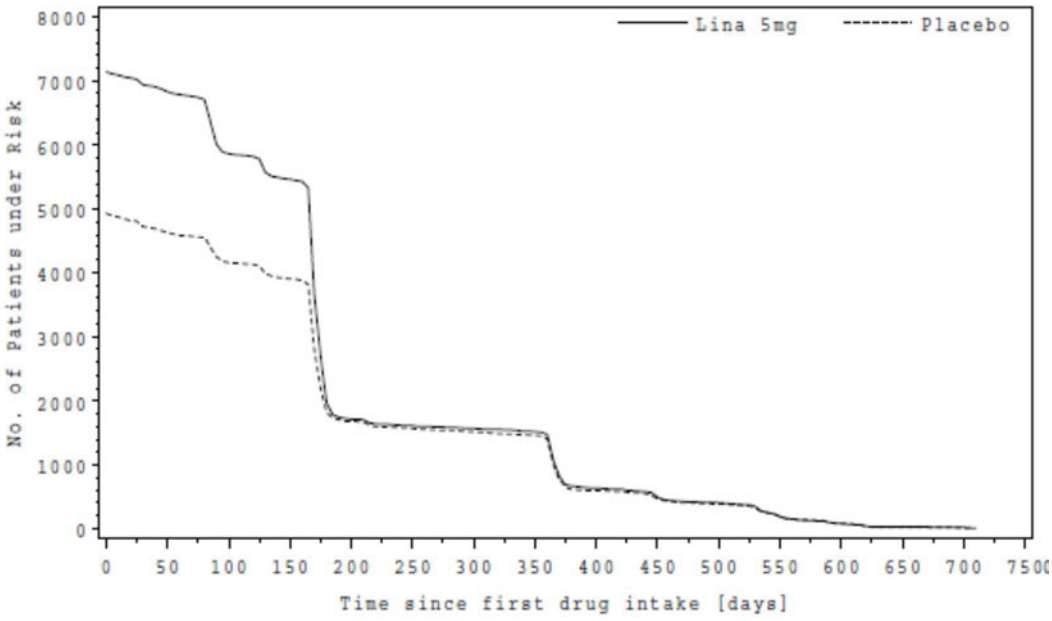
For this RMP, data from the clinical development programmes of linagliptin and linagliptin/metformin were analysed using the SAF-2 (linagliptin) and SEA-2 (linagliptin+metformin) datasets comprising the randomised, double-blind, placebo-controlled trials for each drug. A tabular overview of the analysis sets is provided in SIII.Table 1 above.

Further, data from 1218.22 and 1218.74, long-term CV safety (and renal microvascular outcome for 1218.22) trials in patients with T2DM at high vascular risk, have been analysed.

SIII.1 RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES WITH LINAGLIPTIN 5 MG IN PATIENTS WITH T2DM (SAF-2)

SAF-2 comprised in total 4936 patients receiving placebo and 7136 patients receiving linagliptin; 12 072 patients overall (data source: data on file, 8-05-output-rmp-2017-final, Table 3.1.9). A graphical overview on exposure by duration is provided in the figure below. Cumulative exposure is shown by duration in SIII.Table 2.

SIII.Figure 1 Exposure to randomised study medication (SAF-2)



Patients under Risk

Placebo	4936	4639	4152	3901	1686	1571	1518	1466	585	460	384	189	79	17	9
Lina 5mg	7136	6830	5868	5472	1718	1613	1572	1524	626	481	397	185	71	20	14

Data source: data on file, 8-05-output-rmp-2017-final, Figure 3.1.10

SIII.Table 2 Exposure to study medication – TS (SAF-2)

	Placebo		Linagliptin	
Exposure Categories	Number. of patients N (%)	PY	Number of patients, N (%)	PY
≥1 day	4936 (100.0)	3133.4	7136 (100.0)	4071.1
≥2 weeks	4857 (98.4)	3131.9	7066 (99.0)	4069.9
≥4 weeks	4808 (97.4)	3129.4	7009 (98.2)	4066.7
≥12 weeks	4502 (91.2)	3087.2	6610 (92.6)	4005.3
≥24 weeks	3716 (75.3)	2833.1	5157 (72.3)	3550.4
≥52 weeks	1356 (27.5)	1614.6	1416 (19.8)	1686.7
≥1.5 years	198 (4.0)	322.5	198 (2.8)	322.4

Data source: data on file, 8-05-output-rmp-2017-final, Table 3.1.9

An overview on the exposure by age group and gender in SAF-2 is presented in SIII.Table 3. On both treatment arms, the age group ≥50 to <65 years contained approximately half of all patients and the age group ≥75 years was the smallest age group.

SIII.Table 3 Exposure by age group and gender (SAF-2)

Gender	**Placebo**			**Linagliptin**		
Age group [years]	**Number of patients, N (%)**		**Patient-time [years]**	**Number of patients, N (%)**		**Patient-time [years]**
Male						
≤50	714	(25.6)	429.5	976	(24.8)	559.3
>50 to <65	1316	(47.1)	838.4	1784	(45.4)	1019.4
≥65 to <75	604	(21.6)	362.9	949	(24.1)	541.3
≥75	158	(5.7)	99.0	223	(5.7)	122.2
Total	2792	(100.0)	1729.8	3932	(100.0)	2242.3
Female						
≤50	497	(23.2)	320.5	727	(22.7)	391.0
>50 to <65	1021	(47.6)	676.4	1613	(50.3)	941.6
≥65 to <75	505	(23.6)	325.9	715	(22.3)	414.0
≥75	121	(5.6)	80.8	149	(4.7)	82.2
Total	2144	(100.0)	1403.6	3204	(100.0)	1828.9

Data source: data on file, 8-05-output-rmp-2017-final, Table 3.1.11

Exposure by race in SAF-2 is presented in SIII.Table 4.The majority of subjects, approximately 60% in each treatment arm, were White, followed by Asians and a small percentage of Blacks.

SIII.Table 4 Exposure by race (SAF-2)

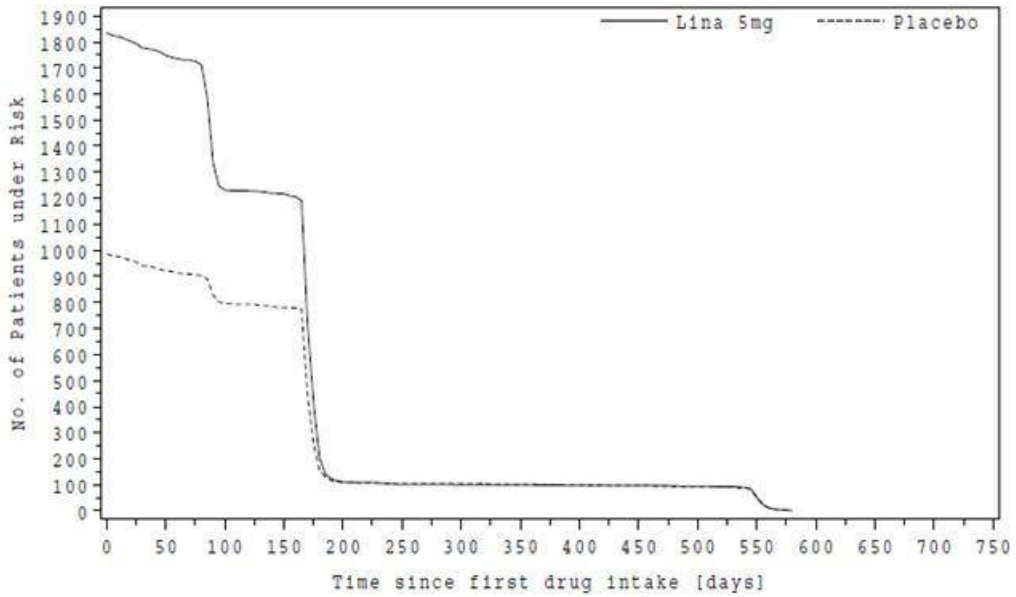
Race	Placebo		Linagliptin	
	Number of patients, N (%)	Patient-time [years]	Number of patients, N (%)	Patient-time [years]
White	2852 (57.8)	1952.3	4060 (56.9)	2488.8
Black	306 (6.2)	176.7	303 (4.2)	175.9
Asian	1778 (36.0)	1004.4	2773 (38.9)	1406.4
Total	4936 (100.0)	3133.4	7136 (100.0)	4071.1

Data source: data on file, 8-05-output-rmp-2017-final, Table 3.1.12

SIII.2 ALL RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS COMPARING LINAGLIPTIN + METFORMIN TO PLACEBO + METFORMIN IN PATIENTS WITH T2DM (SEA-2)

SEA-2 comprised 986 patients receiving placebo + metformin and 1835 patients receiving linagliptin + metformin (data source: data on file, 8-05-output-rmp-2017-final, Table 3.2.1). Cumulative exposure is shown by duration in SIII.Table 5. In both treatment groups, most patients were treated for ≥24 weeks (patient-time placebo + metformin 460.9 years, linagliptin + metformin 647.3 years). A graphical overview on exposure to randomised study medication is provided in the figure below.

SIII.Figure 2 Exposure to randomised study medication - TS (SEA-2)



Patients under Risk

Placebo	986	922	795	781	108	105	105	102	99	96	91	54
Lina 5mg	1835	1749	1232	1217	112	101	100	99	97	97	94	51

Data source: data on file 8-05-output-rmp-2017-final, Figure 3.2.2.

SIII.Table 5 Exposure to study medication - TS (SEA-2)

	Placebo + metformin		**Linagliptin + metformin**	
Exposure Categories	Number of patients, N (%)	PY	Number of patients, N (%)	PY
≥1 day	986 (100.0)	509.7	1835 (100.0)	808.1
≥2 weeks	972 (98.6)	509.4	1815 (98.9)	807.7
≥4 weeks	954 (96.8)	508.5	1789 (97.5)	806.3
≥12 weeks	899 (91.2)	501.2	1677 (91.4)	787.5
≥24 weeks	758 (76.9)	460.9	1152 (62.8)	647.3
≥52 weeks	101 (10.2)	149.5	98 (5.3)	146.8
≥1.5 years	63 (6.4)	95.8	64 (3.5)	97.2

Data source: data on file, 8-05-output-rmp-2017-final, Table 3.2.1

Overall, the gender distribution was comparable across age categories in both treatment groups. About half of the patients in each treatment group were >50 to <65 years of age. Few patients were 75 years or older (data source: data on file, 8-05-output-rmp-2017-final, Table 3.2.3). Further details are summarised in SIII.Table 6.

SIII.Table 6 Exposure by age group and gender – TS (SEA-2)

Gender	**Placebo + Metformin**			**Linagliptin + Metformin**		
Age group [years]	**Number of patients, N (%)**		**Patient-time [years]**	**Number of patients, N (%)**		**Patient-time [years]**
Male						
≤50	198	(34.9)	103.5	307	(30.3)	146.7
>50 to <65	263	(46.3)	133.1	479	(47.3)	203.1
≥65 to <75	101	(17.8)	50.3	189	(18.7)	82.2
≥75	6	(1.1)	3.4	37	(3.7)	13.7
Total	568	(100.0)	290.3	1012	(100.0)	445.8
Female						
≤50	124	(29.7)	73.7	233	(28.3)	100.3
>50 to <65	207	(49.5)	105.4	418	(50.8)	195.4
≥65 to <75	77	(18.4)	35.7	144	(17.5)	56.8
≥75	10	(2.4)	4.7	28	(3.4)	9.8
Total	418	(100.0)	219.4	823	(100.0)	362.3

Data source: data on file, 8-05-output-rmp-2017-final, Table 3.2.3

Both treatment groups were comparable with regard to race at baseline. About half of the patients were White and half were Asian, with few Black patients (SIII.Table 7).

SIII.Table 7 Exposure by race – TS (SEA-2)

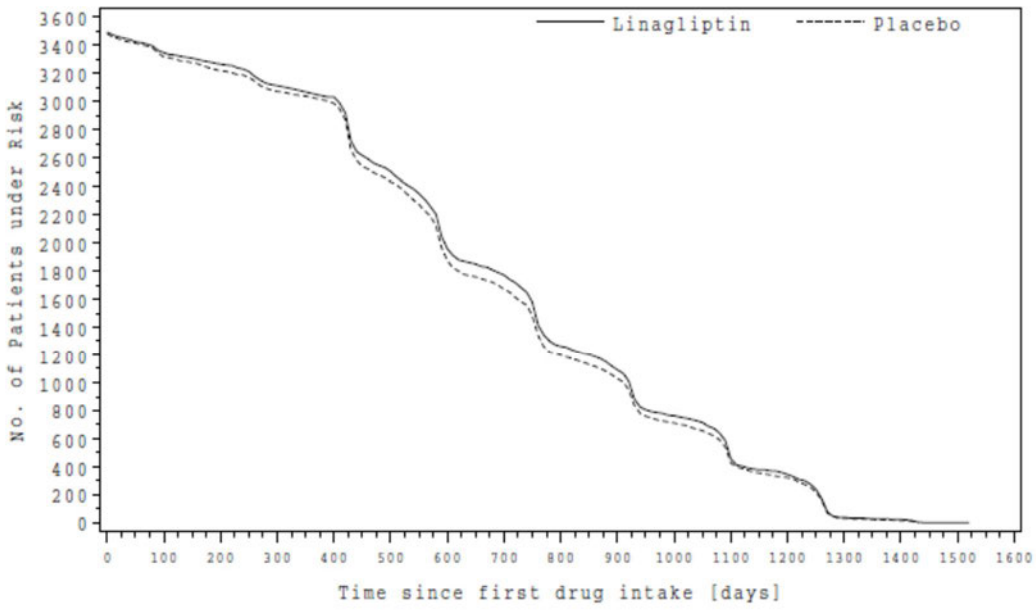
	Placebo + Metformin			Linagliptin + Metformin		
	Number of patients, N (%)		Patient-time [years]	Number of patients, N (%)		Patient-time [years]
Race, N (%)						
White	443	(44.9)	235.0	958	(52.2)	409.2
Black	5	(0.5)	2.9	11	(0.6)	5.5
Asian	538	(54.6)	271.8	866	(47.2)	393.3
Total	986	(100.0)	509.7	1835	(100.0)	808.1

Data source: data on file, 8-05-output-rmp-2017-final, Table 3.2.4

SIII.3 CLINICAL TRIAL 1218.22 LONG-TERM CV SAFETY AND RENAL MICROVASCULAR OUTCOME STUDY

6979 patients were exposed to randomised study drug in 1218.22, including 3494 exposed to linagliptin, and 3485 to placebo. A graphical overview on the exposure is presented in SIII.Figure 3 below. Cumulative exposure is shown by duration in SIII.Table 8. Almost half of the patients had been exposed to randomised study drug for ≥2.0 years.

SIII.Figure 3 Exposure to randomised study medication (1218.22)



Patients under Risk

Linagliptin	3494	3347	3268	3116	3033	2504	1955	1772	1263	1089	762	455	343	38	22	1
Placebo	3485	3317	3219	3074	2987	2434	1872	1672	1196	1028	711	425	321	31	15	

Data source: data on file, 8-05-output-rmp-carmelina-2018-06-11, Figure 1.2

SIII.Table 8 Exposure to study medication 1218.22

	Placebo		Linagliptin	
Exposure Categories	Number of patients, N (%)	PY	Number of patients, N (%)	PY
≥1 day	3485 (100.0)	6585.9	3494 (100.0)	6766.2
≥2 weeks	3453 (99.1)	6585.5	3467 (99.2)	6765.7
≥4 weeks	3437 (98.6)	6584.5	3456 (98.9)	6765.1
≥12 weeks	3372 (96.8)	6574.0	3388 (97.0)	6754.6
≥24 weeks	3258 (93.5)	6538.5	3295 (94.3)	6725.7
≥52 weeks	3029 (86.9)	6376.4	3059 (87.6)	6555.2
≥1.5 years	2276 (65.3)	5448.1	2357 (67.5)	5689.1
≥2.0 years	1576 (45.2)	4266.5	1678 (48.0)	4545.9
≥2.5 years	987 (28.3)	2981.3	1046 (29.9)	3167.7
≥3.0 years	460 (13.2)	1539.7	487 (13.9)	1634.3
≥3.5 years	47 (1.3)	173.6	51 (1.5)	190.5
≥4.0 years	0 (0.0)	0.0	1 (0.0)	4.2

Data source: data on file, 8-05-output-rmp-carmelina-2018-06-11, Table 1.1

Exposure by age group and gender in trial 1218.22 is presented in SIII.Table 9 below, and exposure by race in SIII.Table 10.

SIII.Table 9 Exposure by age group and gender (1218.22)

Gender	**Placebo**		**Linagliptin**	
Age group [years]	**Number of patients, N (%)**	**Patient-time [years]**	**Number of patients, N (%)**	**Patient-time [years]**
Male				
<65	1005 (44.8)	1867.3	973 (45.3)	1904.2
≥65 to <75	901 (40.2)	1771.6	838 (39.0)	1627.5
≥75 to <80	236 (10.5)	431.1	213 (9.9)	419.8
≥80	100 (4.5)	176.8	124 (5.8)	241.7
Total	2242 (100.0)	4246.7	2148 (100.0	4193.2
Female				
<65	496 (39.9)	934.4	494 (36.7)	935.8
≥65 to <75	494 (39.7)	937.3	567 (42.1)	1100.5
≥75 to <80	161 (13.0)	303.6	189 (14.0)	371.9
≥80	92 (7.4)	163.8	96 (7.1)	164.8
Total	1243 (100.0)	2339.1	1346 (100.0)	2573

Data source: data on file, 8-05-output-rmp-carmelina-2018-06-11, Table 1.3

SIII.Table 10 Exposure by race (1218.22)

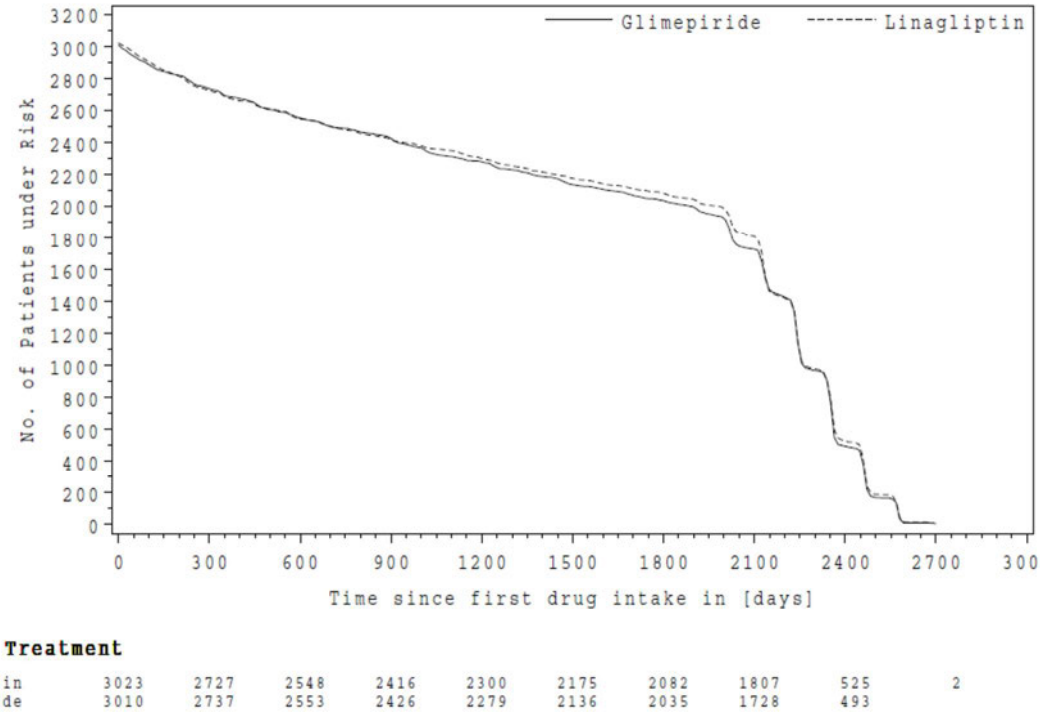
Race	Placebo		Linagliptin	
	Number of patients, N (%)	Patient-time [years]	Number of patients, N (%)	Patient-time [years]
White	2679 (79.5)	5249.6	2827 (80.9)	5469.7
Black	217 (6.2)	368.5	194 (5.6)	340.6
Asian	499 (14.3)	967.8	473 (13.5)	955.9
Total	3485 (100.0)	6585.9	3494 (100.0)	6766.2

Data source: data on file, 8-05-output-rmp-carmelina-2018-06-11, Table 1.4

SIII.4 CLINICAL TRIAL 1218.74 LONG-TERM CV SAFETY STUDY

6033 patients in the TS were exposed to randomised study drug in 1218.74, including 3023 patients exposed to linagliptin, and 3010 patients to glimepiride. A graphical overview on the exposure is presented in SIII.Figure 4 below. Cumulative exposure is shown by duration in SIII.Table 11. Almost half of the patients had been exposed to randomised study drug for ≥6.0 years.

SIII.Figure 4 Exposure to randomised study medication – TS (1218.74)



Data source: data on file, xlinarmp—08—study report body, Figure 1.2

SIII.Table 11 Exposure to study medication 1218.74

	Glimepiride Total = 3010		**Linagliptin** Total = 3023	
Exposure Categories	Number of patients, N (%)	PY	Number of patients, N (%)	PY
≥1 day	3010	14 651.0	3023	14 798.3
≥2 weeks	2986	14 650.6	3005	14 797.9
≥4 weeks	2973	14 649.8	2996	14 797.4
≥12 weeks	2907	14 640.9	2925	14 787.3
≥24 weeks	2831	14 616.3	2837	14 757.8
≥52 weeks	2687	14 509.7	2679	14 645.1
≥1.5 years	2587	14 384.8	2595	14 541.3
≥2.0 years	2491	14 218.9	2487	14 355.6
≥2.5 years	2407	14 024.8	2408	14 176.6
≥3.0 years	2312	13 765.4	2350	14 018.4
≥3.5 years	2233	13 506.7	2258	13 719.0
≥4.0 years	2162	13 239.0	2194	13 478.9
≥4.5 years	2095	12 957.5	2130	13 208.1
≥5.0 years	2019	12 596.5	2065	12 897.6
≥5.5 years	1897	11 947.6	1965	12 367.3
≥6.0 years	1434	9292.0	1431	9294.6
≥6.5 years	508	3473.3	549	3755.9
≥7.0 years	156	1102.2	176	1244.3

Data source: data on file, xlinarmp—08—study report body, Table 1.1

Exposure by age group and gender in trial 1218.74 is presented in SIII.Table 12 below, and exposure by race in SIII.Table 13.

SIII.Table 12 Exposure by age group and gender (1218.74)

Gender	Glimepiride		Linagliptin	
Age group [years]	Number of patients, N (%)	Patient-time [years]	Number of patients, N (%)	Patient-time [years]
Male				
<65	906 (50.9)	4617.1	968 (52.7)	4838.4
≥65 to <75	622 (34.9)	3056.8	641 (34.9)	3148.4
≥75 to <80	190 (10.7)	819.5	175 (9.5)	769.5
≥80	63 (3.5)	258.3	54 (2.9)	214.4
Total	1781 (100.0)	8751.7	1838 (100.0)	8970.6
Female				
<65	596 (48.5)	2998.3	588 (49.6)	2984.0
≥65 to <75	450 (36.6)	2066.2	416 (35.1)	2056.9
≥75 to <80	143 (11.6)	674.8	141 (11.9)	620.4
≥80	40 (3.3)	159.9	40 (3.4)	166.4
Total	1229 (100.0)	5899.3	1185 (100.0)	5827.6

Data source: data on file, xlinarmp—08—study report body, Table 1.3

SIII.Table 13 Exposure by race (1218.74)

	Glimepiride		Linagliptin	
Race	Number of patients, N (%)	Patient-time [years]	Number of patients, N (%)	Patient-time [years]
White	2190 (72.8)	10 617.8	2217 (73.3)	10 802.7
Black	169 (5.6)	663.1	155 (5.1)	583.6
Asian	641 (21.3)	3356.7	642 (21.2)	3396.9
Missing	10 (0.3)	13 3	9 (0.3)	15.0
Total	3010 (100.0)	14 651.0	3023 (100.0)	14 798.3

Data source: data on file, xlinarmp—08—study report body, Table 1.4

SIII.5 REFERENCES

Not applicable

ABBREVIATIONS

CV	Cardiovascular
NA	Not applicable
RMP	Risk management plan

SAF	Safety analysis set (Linagliptin)
SEA	Safety analysis set (Linagliptin+metformin)
TS	Treated set
T2DM	Type 2 diabetes mellitus

MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL TRIALS WITHIN THE DEVELOPMENT PROGRAMME

Hypersensitivity

Reason for exclusion	Hypersensitivity is a listed side effect for Trajenta
Is it considered to be included as missing information?	No
Rationale	Hypersensitivity is a contraindication for Trajenta

MI, stroke, or TIA within 6 months prior to informed consent

Reason for exclusion	Placebo-controlled trials to assess efficacy and safety did not initially enrol a high CV risk population.
Is it considered to be included as missing information?	No
Rationale	An increased risk of adverse CV events with linagliptin was not identified in the 2 prospective long-term CVOTs which enrolled patients with high CV risk (history of MI and stroke). Therefore, this exclusion criterion is not considered missing information

Treatment with systemic steroids

Reason for exclusion	Systemic steroids can be a confounding factor in the assessment of body weight and glucose lowering and thus interfere with the efficacy endpoints.
Is it considered to be included as missing information?	No
Rationale	This concern is applicable only in the clinical trial setting. There is no scientific evidence that would suggest that the safety profile of Trajenta in patients treated with systemic steroids would differ from that in the remaining target population. Therefore, this exclusion criterion is not considered missing information.

Body mass index >40 kg/m^2	
Reason for exclusion	To assess a possible weight effect of linagliptin; thus, interferes with the efficacy endpoints.
Is it considered to be included as missing information?	No
Rationale	The concern is applicable only in the clinical trial setting. There is no scientific evidence that would suggest that the safety profile of Trajenta in patients with a BMI >40 kg/m^2 would differ from that in the remaining target population. Therefore, this exclusion criterion is not considered missing information.

Impaired hepatic function, defined by serum levels of either alanine or aspartate aminotransferase or alkaline phosphatase above 3x the upper limit of normal	
Reason for exclusion	To detect liver disorders during treatment with linagliptin.
Is it considered to be included as missing information?	No
Rationale	There is no scientific evidence that would suggest that the safety profile of Trajenta in patients with impaired hepatic function would differ from that in the remaining target population. Therefore, this exclusion criterion is not considered missing information.

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 adverse reactions with a long latency or those caused by prolonged or cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

SIV.Table 1 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure	
	Number	Person-time
Pregnant women	Not included in the clinical development programme; however, 9 female patients became pregnant during clinical trials with linagliptin or linagliptin/metformin. Additionally, 32 cases have been reported from post-marketing sources for a total of 41 cases of drug exposure during pregnancy from all sources for Trajenta and Jentadueto.	-
Breastfeeding women	Not included in the clinical trial programme	Not applicable
Patients with relevant co-morbidities		
• Patients with severe hepatic impairment	Trial 1218-0027 8 subjects with severe hepatic impairment each received a single dose of linagliptin 5 mg in a study investigating the PK and PD of linagliptin in subjects with different degrees of liver impairment.	--
• Patients with severe renal impairment	Trial 1218-0026 12 patients (6 in each group) with mild or moderate renal impairment received one 5 mg linagliptin tablet once daily for 7 days. 12 patients (6 in each group) with severe renal impairment or end-stage renal disease received a single dose of 5 mg linagliptin. 11 patients with severe renal impairment and T2DM received one 5 mg linagliptin tablet once daily for 10 days. Trial 1218-0043 68 patients with severe renal impairment and T2DM were randomised to receive one 5 mg linagliptin tablet once daily for 52 weeks (range 29 to 396 days [mean 313 days]). Trial 1218-0064 113 patients with moderate to severe renal impairment and T2DM were randomised to receive one 5 mg linagliptin tablet once daily for 52 weeks (mean 337 days).	--

SIV.Table 1 (cont'd) Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure	
	Number	Person-time
• Patients with severe renal impairment (cont'd)	SAF-2 118 subjects (75.7 PY) with severe or end-stage renal impairment received at least 1 dose of linagliptin (5 mg) in randomised, double-blind, placebo-controlled studies with linagliptin. SEA-2 No subjects with severe or end-stage renal impairment received Jentadueto in randomised, double-blind, placebo-controlled studies with linagliptin + metformin. Trial 1218-0022 (CARMELINA) 516 subjects with severe renal impairment and 1684 patients with moderate (stage 3a or 3b) received one 5 mg linagliptin tablet once daily. Median exposure in subjects with severe renal impairment was 596 days (range 1-1432 days). Median exposure in subjects with moderate renal impairment was 739 days (range: 1-1524 days). Trial 1218-0074 (CAROLINA) 16 subjects with severe renal impairment and 576 patients with moderate (stage 3a or 3b) received one 5 mg linagliptin tablet once daily. Median exposure in subjects with severe renal impairment was 797 days (range 35-2458 days). Median exposure in subjects with moderate renal impairment was 2113 days (range: 1-2701 days).	--
• Patients with established CV disease	Trial 1218-0022 (CARMELINA) Results from this trial in 6979 patients (3494 treated with linagliptin 5 mg) with T2DM and high CV risk demonstrated non-inferiority of linagliptin versus placebo for the primary endpoint, which was time to first occurrence of CV death, non-fatal MI, or non-fatal stroke (3-point MACE). There were also no differences between treatment groups with regard to 4P-MACE, CV death, all-cause mortality, MI-related endpoints, or heart failure endpoints.	

SIV.Table 1 (cont'd) Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure	
	Number	Person-time
• Patients with established CV disease (cont'd)	Trial 1218-0074 (CAROLINA) Results from this trial in 6033 patients (3023 treated with linagliptin 5 mg) with T2DM and high CV risk demonstrated non-inferiority of linagliptin vs glimepiride for the primary endpoint, which was time to first occurrence of CV death, non-fatal MI, or non-fatal stroke (3-point MACE). There were also no differences between treatment groups with regard to 4P-MACE, CV death, all-cause mortality, MI-related endpoints or heart failure endpoints.	
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical trial programme	Not applicable
Population with relevant different ethnic origin	See SIII.Table 4, SIII.Table 7, SIII.Table 10, and SIII.Table 13 for information on ethnic origin from safety pools SAF-2 and SEA-2, and from clinical trials 1218-0022 and 1218-0074, respectively.	--
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical trial programme	Not applicable
Other		
• Paediatric patients	A clinical trial (1218-0091) did not establish efficacy in paediatric patients 10 to 17 years of age. Therefore, treatment of children and adolescents with linagliptin is not recommended. Linagliptin has not been studied in paediatric patients under 10 years of age.	--
• Elderly patients (>80 years)	Elderly patients were included in the clinical trials. However, prior to the CV safety studies 1218-0022 and 1218-0074 (both completed), linagliptin had not been investigated in patients >80 years. Trial 1218-0022 (CARMELINA) In this trial, 412 patients ≥80 years of age were treated with at least 1 dose of study medication, including 220 patients who received linagliptin 5 mg.	1218-0022: Lina: 406.5 PY

SIV.Table 1 (cont'd) Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure	
	Number	Person-time
• Elderly patients (>80 years) (cont'd)	Trial 1218-0074 (CAROLINA) In this trial, 197 patients ≥80 years of age were treated with at least 1 dose of study medication, including 94 patients who received linagliptin 5 mg.	1218-0074: Lina: 380.8 PY

Data source: Trajenta/Jentadueto PBRER (reporting interval 03 May 2021 to 02 May 2024) [s00130773-01], Trajenta RMP v 11.0 [s00016631-17] Module SIV Sections SIV.3.1, SIV.3.2, SIV.3.3, SIV.3.4, SIV.3.5, SIV.3.6, 1218-0026 [U10-1467-02], 1218-0043 [U11-3170-01], 1218-0091 (main and ancillary) [c38245139-01, c38245139-01], 1218-0064 [U13-1283-01], 8-05-output-rmp-carmelina-2018-06-25 [c25086316] tables 1.3 and 1.5, 1218-0022 [c22196815-03], 1218-0074 [c23238241-01], 8-05-output-rmp-carolina-2019-02-04 [c26539516], tables 1.3 and 1.5

SIV.4 REFERENCES

SIV.4.1 Published references

Not applicable.

SIV.4.2 Unpublished references

c22196815-03 A multicenter, international, randomized, parallel group, double-blind, placebo-controlled CArdiovascular Safety & Renal Microvascular outcomE study with LINAgliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk. CARMELINA. 1218-0022. 22 Apr 2020.

c23238241-01 A multicentre, international, randomised, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk. CAROLINA. 1218-0074. Mar 2019.

c25086316 8-05-output-rmp-carmelina-2018-06-25. 25 Jun 2018

c26539516 8-05-output-rmp-carolina-2019-02-04. 4 Feb 2019

c38245139-01 A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus (DINAMO™ main trial). 1218-0091. 10 Nov 2022.

c41705319-01	A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus (DINAMO™ Mono, ancillary trial). 1218-0091. 19 Oct 2023.
s00016631-17	Risk Management Plan for Linagliptin Type 2 diabetes mellitus, Version 11.0. 30 Mar 2017.
s00130773-01	Periodic Benefit-Risk Evaluation Report for Linagliptin (Trajenta) and Linagliptin + Metformin (Jentadueto), Reporting Period from 03 May 2021 to 02 May 2024. dd mmm yyyy
U10-1467-02	Pharmacokinetics, pharmacodynamics, safety and tolerability of single and multiple 5 mg doses of BI 1356 tablets in patients with different degrees of renal impairment in comparison to subjects with normal renal function in a monocentric, open, parallel-group, phase I trial. 1218-0026. 16 Apr 2010.
U11-3170-01	A phase III, randomised, double-blind, placebo-controlled, parallel group, safety and efficacy study of BI 1356 (5 mg), compared to placebo. 1218-0043. 05 May 2011.
U13-1283-01	A phase III, randomised, double-blind, placebo-controlled parallel group safety and efficacy study of linagliptin (5 mg administered orally once daily) over 12 weeks followed by a 40 week double-blind extension period (placebo patients switched to glimepiride) in drug naive or previously treated type 2 diabetic patients with moderate to severe renal impairment and insufficient glycaemic control. 1218-0064. 04 Mar 2013.

ABBREVIATIONS

BMI	Body mass index
CV	Cardiovascular
EMA	European Medicines Agency
MACE	Major cardiac adverse event
MI	Myocardial infarction
PY	Patient years
RMP	Risk management plan
SAF	Safety analysis set (linagliptin)
SEA	Safety analysis set (linagliptin+metformin)
T2DM	Type 2 diabetes mellitus
TIA	Transient ischaemic attack

MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

SV.1.1 Method used to calculate exposure

The method of estimation of patient exposure to the marketed drug is based on worldwide ex-factory sales (i.e. wholesale figures). It is assumed that all tablets have been used by the patients. It is also assumed that each patient was treated with 1 tablet per day (Trajenta), or 2 tablets per day (Jentadueto IR) or 1 or 2 tablets per day (Jentadueto XR) based on the metformin dose required for treatment. The total days of medication is calculated by dividing the total number of tablets sold (ex-factory sales) by the number of tablets taken per day. The total number of days of medication is then divided by 365.25 in order to calculate the total patient exposure in patient-years.

SV.1.2 Exposure

SV.1.2.1 Trajenta

The overall cumulative marketed patient exposure to Trajenta is estimated to be 35 965 901 PY for the time period 02 May 2011 (international birthdate) to 30 Apr 2024.

As there is only 1 indication and formulation for Trajenta, a presentation by these variables is not applicable. A presentation of the overall exposure by region and EU country is presented in the table below:

SV.Table 1 Cumulative exposure from marketing experience by region for Trajenta up to 30 Apr 2024

Region / country	Cumulative exposure [PY]
[redacted]	[redacted]

SV.Table 1 (cont'd) Cumulative exposure from marketing experience by region for Trajenta up to 30 Apr 2024

Region / country	Cumulative exposure [PY]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Total	**35 965 901**

Data source: data on file, ER-031 Trajenta exposure (2024 04)

Exposure data by gender, age and/or indication are not available for Trajenta.

SV.1.2.2 Jentadueto

The overall cumulative marketed patient exposure to Jentadueto (IR and XR formulations) is estimated to be 7 237 853 PY for the time period 01 Feb 2012 (international birthdate) to 30 Apr 2024.

A presentation of the overall exposure by region and EU country is presented in the table below:

SV.Table 2 Cumulative exposure from marketing experience by region for Jentadueto up to 30 Apr 2024

Region / country	Cumulative exposure [PY]
[redacted]	[redacted]

SV.Table 2 (cont'd) Cumulative exposure from marketing experience by region for Jentadueto up to 30 Apr 2024

Region / country	Cumulative exposure [PY]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Total	**7 237 853**

Data source: data on file, ER-015 Jentadueto exposure (2024 04)

Exposure data by gender, age and/or indication are not available for Jentadueto.

SV.2 REFERENCES

Not applicable.

ABBREVIATIONS

EEA	European Economic Area
EU	European Union
IR	Immediate release
PY	Patient years
UK	United Kingdom
US	United States
XR	Extended release

MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Pharmacological properties, non-clinical, and clinical data do not indicate an impact on the central nervous system suggestive for stimulant, depressant, hallucinogenic, or mood-elevating effects. Abuse for illegal purpose is not expected with linagliptin. The speed and magnitude of weight loss observed in the linagliptin clinical trials makes the potential for abuse unlikely.

SVI.2 REFERENCES

Not applicable.

ABBREVIATIONS

Not applicable.

MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

An overview of the safety concerns identified at the time of first authorisation is provided for Trajenta in SVII.Table 1. The concerns shown are based on RMP version 2.0 because this version reflects the addition of 5 topics (paediatric patients, pregnant and lactating patients, hepatic impaired patients, oncological adverse reactions, and idiosyncratic reactions) as missing information based on EMA's assessment of RMP version 1.0.

SVII.Table 1 Summary of safety concerns for Trajenta

Important identified risks	Hypoglycaemia (as add on to metformin and sulfonylurea) Pancreatitis
Important potential risks	Skin lesions
Missing information	Safety in subpopulations • High risk patients with recent CV events • Old patients (>80 years) • Severe renally impaired patients • Paediatric patients • Pregnant and lactating patients • Hepatic impaired patients • Oncological adverse reactions • Idiosyncratic reactions

Data source: Linagliptin RMP version 2.0 [U10-1739-02]

The safety concerns identified in the Jentadueto RMP at the time of authorisation are presented in SVII.Table 2.

SVII.Table 2 Summary of safety concerns for Jentadueto

Important identified risks	Hypoglycaemia (linagliptin/metformin and sulphonylurea) Pancreatitis Lactic acidosis
Important potential risks	Skin lesions Hypersensitivity reactions Infections Worsening of renal function
Important missing information	Safety in subpopulations • high risk patients with recent CV events • old patients (> 80 years) • paediatric patients • pregnant and lactating patients • oncological adverse reactions • idiosyncratic reactions • immunological adverse reactions • concomitant P-gp and CYP3A4 inhibitors

Data source: Jentadueto RMP version 2.0 [U11-1769-02]

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

The RMP is being updated to remove all remaining important risks and missing information topics. Based on the cumulative information gathered from non-clinical, clinical, and post-marketing sources, the following changes to the safety concerns are proposed in this RMP:

Important identified risks
The following topic will be removed as important identified risks:
- Pancreatitis

Important potential risks
The following topic will be removed as an important potential risk:
- Pancreatic cancer

Missing information
The following topic will be removed as missing information:
- Pregnant or breastfeeding women

SVII.2.1 Important identified risks to be demoted

SVII.2.1.1 Pancreatitis

Acute pancreatitis has been raised as a possible adverse effect of DPP-4 inhibitors but there is no consensus about the potential mechanism and pathology. One line of thought is directed towards involvement of low-grade asymptomatic inflammatory changes in the exocrine pancreas as seen in some studies as elevations in serum amylase or lipase. Diabetes mellitus itself and accompanying complications and habits such as alcohol drinking, smoking, obesity, etc. might adversely affect the pancreas [R13-5153, R10-5365, R10-5590, R10-5391].

SVII.2.1.1.1 Clinical data

SAF-2
Randomised, double-blind, placebo-controlled studies with linagliptin 5 mg in patients with T2DM (SAF-2)

In the SAF-2 dataset of randomised, double-blind, placebo-controlled clinical trials with linagliptin 5 mg (SVII.Table 3) and in the placebo-controlled CVOT CARMELINA (SVII.Table 4), pancreatitis was reported infrequently, but at a slightly higher rate in the linagliptin group than in the placebo group.

SVII.Table 3 Overview on pancreatitis (SAF-2)

	Placebo	Linagliptin
Number of patients treated, N (%)	5038 (100.0)	7240 (100.0)
Total overall time at risk (PY)	3259.9	4219.8
Patients with pancreatitis, risk rate N (%)	4 (0.1)	8 (0.1)
95% CI	[0.0, 0.2]	[0.1, 0.2]
Incidence rate/100 PY [95% CI]	0.12 [0.05, 0.32]	0.19 [0.10, 0.37]
Incidence rate ratio[1] [95% CI]	1.88 [0.55, 6.31]	
Risk rate ratio[1] [95% CI]	1.85 [0.55, 6.39]	
Seriousness[2,3], N (%)	4 (100.0)	4 (50.0)
Required hospitalisation	3 (75.0)	3 (37.5)
Prolonged hospitalisation	1 (25.0)	0 (0.0)
Other	0	1 (12.5)
Outcome[2,4], N (%)		
Recovered	4 (100.0)	7 (87.5)
Sequelae	0	1 (12.5)
Intensity[2], N (%)		
Mild	0	3 (37.5)
Moderate	1 (25.0)	3 (37.5)
Severe	3 (75.0)	2 (25.0)

[1]Ratio linagliptin vs. placebo

[2]Percentages are calculated using the number of all patients with pancreatitis as the denominator.

[3]Patients can be counted in more than 1 seriousness category

[4]Outcome categories are mutually exclusive

Data source: cRMP for Trajenta and Jentadueto, version 2.0, Table 23 [s00071559-02]

CARMELINA (1218-0022)

Pancreatitis events were adjudicated by the independent CEC. During the entire observation period in the study, 9 patients (0.3%) in the linagliptin group were confirmed with acute pancreatitis vs 5 patients (0.1%) in the placebo group (SVII.Table 4) (data source, 1218-0022 CTR [c22196815-03], Table 15.3.1.5.3).

SVII.Table 4 Patients with CECP-confirmed pancreatitis by treatment in trial 1218-0022 (CARMELINA) - TS

	Placebo		Linagliptin	
	N	(%)	N	(%)
Number of patients	3485	(100.0)	3494	(100.0)
Patients with at least 1 pancreatic event	53	(1.5)	92	(2.6)
Patients with acute pancreatitis	5	(0.1)	9	(0.3)
Without organ failure	5	(0.1)	5	(0.1)
With organ failure	0	-	4	(0.1)
Patients with chronic pancreatitis	3	(0.1)	2	(0.1)

Data source: 1218-0022 CTR [c22196815-03], Table 15.3.1.5: 3

4 of the 9 patients in the linagliptin group had events that were assessed by the CEC as acute pancreatitis with organ failure (none were reported in the placebo group) and this assessment was based on other concomitant AEs such as acute respiratory distress syndrome, renal failure, and/or shock or fatal outcome (2 cases had a reported fatal outcome). Medical review of these cases showed other confounding conditions such as histoplasmosis, morbid obesity, complicating sepsis, and acute or chronic renal failure, which likely contributed to these concomitant AEs or fatal outcomes. The incidence of adjudicated chronic pancreatitis was low and similar between the treatment groups (0.1% in each group).

CAROLINA (1218-0074)

In the CVOT CAROLINA, comparing linagliptin to glimepiride, investigator-confirmed pancreatitis events were similar in the linagliptin group and in the glimepiride group during the observation period of the trial including any event after the first dose of trial medication up to trial end. (SVII.Table 5). Acute pancreatitis was confirmed for 15 patients in the linagliptin and 16 patients in the glimepiride group (0.5% each). Of those, 1 patient treated with linagliptin and 2 patients treated with glimepiride had organ failure as assessed by the CECP. There was no fatal outcome of acute pancreatitis in the linagliptin group; 1 out of the 2 organ failure events in the glimepiride group was fatal. Chronic pancreatitis was confirmed for 3 patients (0.1%) in the linagliptin group and none of the patients in the glimepiride group (data source: 1218-0074 CTR [c23238241-01], Table 12.1.4.5: 1).

SVII.Table 5 Patients with CECP-confirmed pancreatitis by treatment in trial 1218-0074 (CAROLINA) - TS

	Glimepiride		Linagliptin	
	N	(%)	N	(%)
Number of patients	3010	(100.0)	3023	(100.0)
Patients with acute pancreatitis	16	(0.5)	15	(0.5)
Without organ failure	15	(0.5)	14	(0.5)
With organ failure	2	(0.1)	1	(0.0)
Patients with chronic pancreatitis	0		3	(0.1)

Data source: 1218-0074 CTR [c23238241-01], Table 12.1.4.5:1

The 3 cases of CECP-confirmed chronic pancreatitis were assessed as not related to trial medication by the investigator. 2 patients had their last dose of trial medication 2 years and 4 years prior to AE onset. The patient in the 3rd case was on treatment at AE onset (exposure of 17 months) and had a history of increased alcohol consumption. A Cox regression analysis was performed for the time to first occurrence of CECP-confirmed acute pancreatitis. The Kaplan-Meier estimates showed that the probability of first onset of acute pancreatitis was similar for patients in both treatment groups (p=0.85) (data source: 1218-0074 CTR [c23238241-01], Figure 15.3.1.5: 1 and Table 15.3.1.5: 4).

SVII.2.1.1.2 Post-marketing data

Trajenta
In the cumulative post-marketing data (DLP 02 May 2024) presented in the latest Trajenta/Jentadueto PBRER [s00130773-01], 613 cases reporting 628 events of pancreatitis were identified using the SMQ “acute pancreatitis” (narrow) and the MedDRA (v. 26.1) PT “Pancreatitis chronic”. The most frequently reported PTs in these cases were ‘Pancreatitis’ in 65% of cases and ‘Pancreatitis acute’ in 35% of cases (data on file, Trajenta, Table 52). Pancreatitis was serious in 92% of cases and fatal in 21 cases (3.4%). Details on the fatal cases are presented in the above-mentioned PBRER.

Jentadueto
The cumulative search resulted in 63 cases. The most frequently reported PTs were ‘Pancreatitis’ in 68% of cases and ‘Pancreatitis acute’ in 30% of cases. Pancreatitis was serious in 87% of cases. There were no fatal events of pancreatitis (data on file, Jentadueto, Tables 31, 37, 38, and 39).

Conclusion on post-marketing data
Overall, the review of post-marketing events representative of pancreatitis reported cumulatively did not identify a new safety concern or a change in the current understanding of the identified risk of pancreatitis.

Overall conclusion
Cumulative data provide no new information that has an impact on the characterisation of this safety concern. The risk of pancreatitis is considered to be well-addressed in the current CCDSs of both Trajenta and Jentadueto, which list pancreatitis as an undesirable effect and advise that linagliptin should be discontinued if pancreatitis is suspected. Since pancreatitis is still considered key to the benefit-risk assessment of linagliptin-containing products, this topic will continue to be presented as part of the future PBRERs; however, in line with the GVP Module V Revision 2 recommendations, there is no reasonable expectation that existing or additional pharmacovigilance activities (e.g. PASS) could further characterise the safety profile of Trajenta or Jentadueto with respect to pancreatitis. Therefore, as routine monitoring is considered sufficient, Boehringer Ingelheim proposes to remove pancreatitis as an important identified risk from the EU RMP. However, any new information concerning the risk will continue to be presented in future PBRERs.

SVII.2.2 Important potential risks to be demoted

SVII.2.2.1 Pancreatic cancer

Pancreatic cancer was added as a new important potential risk at the request of the EMA CHMP (please refer to CHMP's recommendation of the Art.5(3) procedure EMA/671092/2013, dated 30 Oct 2013).

The role of DPP-4 in tumour biology

As well as its effect in the treatment of diabetes, CD26/DPP-4 also plays an important role in tumour biology and is useful as a marker for various cancers, with its levels either on the cell surface or in the serum increased in some neoplasms and decreased in others. Many reviews have discussed the non-enzymatic role of CD26/DPP-4 as an extracellular anchorage for ADA in cancer and the potential usefulness of this protein in therapeutics and diagnostics. The ADA-CD26 complexes may participate in cell-to-cell contacts or, more probably in this context, through the catalysis of adenosine to inosine. Proliferating cells accumulate high extracellular concentrations of adenosine, a purine nucleoside found within the interstitial fluid of solid tumours, which may be toxic or influence the proliferative potential of a cell, depending on the relative expression and type of adenosine receptor. Therefore, the different levels of the cell-surface CD26-ADA complex and relative expression of adenosine receptors on a tumour cell may lead to the generation of tumour subclones, as well as its participation in the well-known adenosine inhibition of cell-mediated immune responses to tumour cells. Other pro-oncogenic activities may be related to the recently described CD26-ADA-plasminogen ternary complex. Binding of plasminogen to cell-surface receptors promotes its conversion to plasmin, which is required for proteolysis of the extracellular matrix in several physiological and pathological processes, including cell migration, tumour cell invasion, and metastasis [R13-2885].

DPP-4 enzymatic activity is high in patients with hepatic cancer, hepatitis, osteoporosis, cholestasis, and other liver diseases. On the other hand, the mean DPP-4 activity remains unchanged in metastatic bone disease, oesophagus, gall bladder, chronic myelocytic leukaemia or leiomyosarcoma cancers, in allergic asthma, celiac disease, and adult T-cell

leukaemia, although serum DPP-4 in the latter is strongly correlated with the percentage of CD26+ T cells. However, decreased levels of DPP-4 were observed in patients with acute lymphocytic leukaemia, thyroid and oral cancer, advanced gastric carcinoma, hepatitis C infections, inflammatory bowel diseases, T2DM, in healthy smokers, in pregnancy, and in alcoholics and patients suffering from major depression. A reduction in DPP-4 activity has been related to symptoms of depression and anxiety under certain circumstances. Contradictory results were reported for psychologically related eating disorders such as anorexia or bulimia, colorectal cancer, rheumatoid arthritis, lupus erythematosus, and Sjögren syndrome. A reduction in DPP-4 serum levels is being postulated as a biomarker for colorectal cancer [R13-2885].

Pancreatic cancer was added as an important potential risk at the request of the CHMP in the EMA. Recently completed CVOTs for other DPP-4 inhibitors have shown no increase in pancreatic cancer cases in patients treated with DPP-4 inhibitors as compared to those on placebo or active comparator.

SVII.2.2.1.1 Clinical data

Patients with pancreatic cancer were identified using the narrow BicMQ ‘pancreatic neoplasms’. This search also includes the non-specific PT of ‘Pancreatic cyst’. In the CARMELINA and CAROLINA trials, pancreatic events and malignancies were also adjudicated centrally through an independent, blinded, external CEC.

SAF-2
Randomised, double-blind, placebo-controlled studies with linagliptin 5 mg in patients with T2DM (SAF-2)

SVII.Table 6 provides an overview on pancreatic cancer (SAF-2).1 patient in the linagliptin treatment arm had an event of Pancreatic carcinoma stage II.

SVII.Table 6 Overview on pancreatic cancer (SAF-2)

	Placebo	Linagliptin
Number of patients treated, N (%)	5038 (100.0)	7240 (100.0)
Total overall time at risk (PY)	3260.0	4222.8
Patients with pancreatic cancer, risk rate N (%)	0	1 (0.00)
95% CI	N/A	[0.0, 0.1]
Incidence rate/100 PY [95% CI]	0.00 [0.00, 0.12]	0.02 [0.00, 0.13]
Incidence rate ratio[1] [95% CI]	N/A	
Risk rate ratio[1] [95% CI]	N/A	
Seriousness[2,3], N (%)	0	1 (100.0)
Required hospitalisation	0	1 (100.0)
Outcome[2,4], N (%)		
Not yet recovered	0	1 (100.0)
Intensity[2], N (%)		
Moderate	0	1 (100.0)

[1]Ratio linagliptin vs. placebo

[2]Percentages are calculated using the number of all patients with pancreatic cancer as the denominator

[3]Patients can be counted in more than 1 seriousness category

[4]Outcome categories are mutually exclusive

Data source: cRMP for Trajenta and Jentadueto, version 2.0, Table 31 [s00071559-02]

CARMELINA (1218-0022)

During the study period, 11 patients (0.3%) in the linagliptin group and 6 patients (0.2%) in the placebo group had an investigator-reported pancreatic cancer event. (data source: 1218-0022 CTR [c22196815-03], Table 15.3.1.8.6); these include cases of neoplasm or malignancy and do not include cysts.

All these cases were adjudicated by an independent Pancreatic Event Committee in a blinded data set. From the investigator-reported pancreatic cancer cases stated above, 11 patients (0.3%) in the linagliptin group and 4 patients (0.1%) in the placebo group had an adjudication-confirmed pancreatic malignancy during the study (data source: 1218-0022 CTR [c22196815-03], Table 15.3.1.5.3).

The time to onset for the majority of adjudication-confirmed pancreatic cancer cases was relatively short and ranged from 5 to 36 months. Independent blinded assessment by the Oncology Assessment Committee for causality determination with study medication resulted in 1 patient in the linagliptin group and 1 patient in the placebo group with an event that was assessed as possibly related to treatment (data source, data on file, 1218-0022 CTR, Listing 16.2.7.9).

CAROLINA (1218-0074)
The proportions of patients reported with pancreatic cancer by the investigator were similar in both treatment groups (linagliptin 0.6%; glimepiride 0.8%). There was also no imbalance for any reported PTs.

As part of the adjudication of pancreatic events, the CECP was to confirm whether the event was pancreatic cancer. There were 16 patients (0.5%) in the linagliptin treatment group and 24 patients (0.8%) in the glimepiride group with at least 1 CECP-confirmed pancreatic cancer during the trial; of these, 9 patients (0.3%) in the linagliptin group and 13 patients (0.4%) in the glimepiride group had pancreatic cancer that was assessed as possibly related to study treatment by the Oncology Assessment Committee. (data source: 1218-0074 CTR [c23238241-01], Table 12.1.5.1: 3 and 12.1.5.1: 4).

Conclusion on clinical data
Very few cases of pancreatic cancer have been reported in pooled clinical studies (SAF-2) and in the recently completed cardiovascular safety studies 1218-0022 and 1218-0074. During the observation period in CARMELINA, a higher proportion of patients receiving linagliptin had an adjudication-confirmed pancreatic malignancy compared with the placebo group, while in CAROLINA, a numerically lower number of patients in the linagliptin group was reported with CECP-confirmed pancreatic cancer compared with the glimepiride group; however, in both studies, the overall incidence was low.

SVII.2.2.1.2 Post-marketing data

Trajenta
In the cumulative post-marketing data (DLP 02 May 2024) presented in the latest Trajenta/Jentadueto PBRER [s00130773-01], 108 cases reporting 110 events of pancreatic cancer were identified using the narrow BIcMQ ‘Pancreatic neoplasms’ (MedDRA version 26.1). The most frequently reported PT in these cases was ‘Pancreatic carcinoma’ in 77% of cases. Pancreatic cancer was serious in all but 2 cases and fatal in 25% of cases. (data on file, Trajenta, tables 68 and 69). TTO was reported for 48 of the 108 cases (45%). Of these 48 cases, TTO was 1 year or more in 22 cases (data on file, Trajenta Table 71). Of these 22 cases, 1 case describes a benign pancreatic neoplasm and 1 case a pancreatic enzyme abnormality with no mention of malignancy. The remaining 20 cases with TTO >1 year either provided insufficient information to allow for a complete clinical assessment, or reported other risk factors (e.g. excessive alcohol consumption, smoking, obesity) that could have contributed to the development of pancreatic cancer (data on file, 03_case_Pancreatic neoplasms_CSMR and 03_drugevent_Pancreatic neoplasms_CSMR).

Jentadueto
The cumulative search identified 11 cases, all from spontaneous sources. The most frequently reported PT was ‘Pancreatic carcinoma’ in 8 cases. ‘Cystadenocarcinoma pancreas’, ‘Pancreatic carcinoma metastatic’, and ‘Pancreatic mass’ were the PTs reported in the other 3 cases. Pancreatic cancer was serious in all cases and fatal in 2 cases. No case had a TTO > 1 year. (data on file, Jentadueto, Tables 61, 67, 68, 69, and 71).

Conclusion on post-marketing data
Cumulative and interval data provide no new information that has an impact on the characterisation of this safety concern.

Overall conclusion
Based on the current information on linagliptin and considering that there is no reasonable expectation that existing or additional pharmacovigilance activities (e.g. PASS) could further characterise the safety profile of Trajenta or Jentadueto with respect to pancreatic cancer, Boehringer Ingelheim proposes to remove 'Pancreatic cancer' as an important potential risk from the EU RMP. However, any new information concerning the risk will continue to be presented in future PBRERs.

SVII.2.3 Missing information to be removed

SVII.2.3.1 Pregnancy / breastfeeding

Neither linagliptin nor the linagliptin/metformin FDC have been studied in pregnancy or nursing neonates/infants. There are no adequate and well-controlled studies in pregnant women. As a precaution, women should not be treated with linagliptin or linagliptin/metformin during pregnancy or breastfeeding.

There was no suggestion of a teratogenic effect attributable to the co-administration of linagliptin and metformin [U10-2448-01]. Metformin was not teratogenic in rats at a dose of 200 mg/kg/day associated with a systemic exposure of 4 times the maximum recommended human dose (2000 mg metformin). At higher doses inducing dysglycaemia in the tested non-diabetic animals (500 and 1000 mg/kg/day, associated with 11 and 23 times the maximum recommended human dose), teratogenicity of metformin was observed [U10-2386-01]. Metformin is excreted with milk in humans.

Animal reproduction studies with linagliptin demonstrated wide safety margins (943-fold MRHD) for fertility, embryonic development and postnatal development of neonates. There was no evidence for teratogenicity up to 943-fold MRHD [U06-2047, U06-1200, U07-1558, U10-1332-01]. In animal studies, linagliptin has been reported to pass across the placenta [U10-1332-01] and into breast milk. It is not known whether linagliptin is excreted into human milk.

In the cumulative post-marketing data (DLP 02 May 2024) presented in the latest Trajenta/Jentadueto PBRER [s00130773-01], a total of 41 relevant cases from all sources were identified based on cases from the Boehringer Ingelheim GSP with pregnancy flag marked as 'Pregnant: Yes' (MedDRA version 26.1). DEDP was reported in patients treated with linagliptin or linagliptin/metformin, in the clinical development programme and from the post-marketing sources.

Trajenta
Cumulatively, 36 cases reporting DEDP were identified. Of these 36 cases, 8 were from clinical trials and 28 from post-marketing sources. Pregnancy outcome was normal full term vaginal birth in 3 cases, abnormal in 11 cases and not (yet) known in the remaining 22 cases.

Available information on pregnancies with abnormal outcome is summarised in the table below. No cases of breast feeding on Trajenta or Jentadueto have been reported to date.

SVII.Table 7 Cumulative summary of Trajenta DEDP cases with abnormal outcomes

Case No.	Maternal age Source	Drug exposure (suspect drugs)	Time of exposure (Trimester)	Pregnancy outcome
1	late 30s CT	Linagliptin 2.5 mg and metformin 1000 mg (free combination)	[redacted]	[redacted]
2	late 30s SP	Linagliptin 5 mg	[redacted]	[redacted]
3	mid 30s CT	Linagliptin 5 mg	[redacted]	[redacted]
4	mid 30s CT	Linagliptin 5 mg + metformin 2000 mg (free combination)	[redacted]	[redacted]
5	late 20s CT	Linagliptin 5 mg + metformin 500 mg (free combination)	[redacted]	[redacted]
6	late 20s SP	Linagliptin 5 mg	[redacted]	[redacted]
7	Unk SP	Linagliptin, glimepiride, metformin	[redacted]	[redacted]
8	early 30s CT	Linagliptin, empaglifozin	[redacted]	[redacted]
9	Unk SP	Linagliptin	[redacted]	[redacted]
10	early 40s SP	Linagliptin 5 mg	[redacted]	[redacted]
11	late 30s SP	Linagliptin	[redacted]	[redacted]

In the above cases, besides diabetes mellitus itself as a risk factor for pregnancy complications, some patients had additional risk factors such as past history of spontaneous abortion, hypertension, or uterine leiomyoma.

Jentadueto

Cumulatively, 5 cases reporting DEDP were identified. Of these 5 cases, 1 was from a clinical trial and 4 from post-marketing sources. 1 of the cases involved paternal exposure at conception; pregnancy outcome was unknown. The other 4 cases involved maternal exposure; outcomes were elective abortions no pathology reported in 2 cases, a healthy baby in 1 case and unknown in 1 case. Available information on pregnancies with abnormal outcome is summarised in the table below.

SVII.Table 8 Cumulative summary of Jentadueto DEDP cases with abnormal outcomes

Case No.	Maternal age Source	Drug exposure (suspect drugs)	Time of exposure (Trimester)	Pregnancy outcome
1	late 20s CT	Linagliptin 2.5 mg and metformin 500 mg (FDC)	[redacted]	[redacted]
2	late 30s SP	Jentadueto (dose unknown)	[redacted]	[redacted]

No new safety concern was identified from cumulative reviews of DEDP cases. Given the limited data from the use of linagliptin in pregnant women, according to the CCDSs, it is preferable to avoid the use of Trajenta or Jentadueto in pregnant women and caution should be exercised when Trajenta is administered to a nursing woman. Jentadueto should not be used during breast feeding as there are no data on safety of breast feeding on Jentadueto available.

Overall conclusion

Pregnancy and Breastfeeding information is considered to be well-addressed in the current CCDSs of both Trajenta and Jentadueto. No additional risk management measures are in place or planned. In line with the GVP Module V Revision 2 recommendations, there is no reasonable expectation that existing or additional pharmacovigilance activities (e.g. PASS) could further characterise the safety profile of Trajenta or Jentadueto with respect to pregnancy/breastfeeding. Therefore, Boehringer Ingelheim proposes to remove this topic from the EU RMP as missing information. Boehringer Ingelheim will continue to routinely monitor this topic and present new relevant information in future PBRERs.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

For Trajenta and Jentadueto, there are no important identified or potential risks, and no missing information.

SVII.4 REFERENCES

SVII.4.1 Published references

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U10-2448-01 BI 1356 (Linagliptin) and Metformin: Study for effects on embryo-fetal development in rats by oral (gavage) administration. 09B138. 26 Oct 2010.

U11-1769-02 Risk Management Plan BI 1356 and Metformin Hydrochloride Version 2.0. 23 Dec 2011.

ABBREVIATIONS

ACE	Angiotensin converting enzyme
AE	Adverse event
AESI	Adverse event of special interest
AR	Adenosine receptor
ADA	Adenosine deaminase
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim customised MedDRA query
BNP	B-type natriuretic peptide
CEC	Clinical Event Committee
CECP	Clinical Event Committee for pancreatic events
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CTR	Clinical Trial Report
CV	Cardiovascular
CYP	Cytochrome P-450
DEDP	Drug exposure during pregnancy
DPP-4	Dipeptidyl peptidase-4
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESRD	End-stage renal disease
EU	European Union
FAMMM	Familial atypical multiple mole melanoma
FDA	Food and Drug Administration
GLP	Glucagon-like peptide
GDSS	Global drug safety system
GSP	Global Safety Platform
HbA_{1c}	Glycated haemoglobin
HHF	Hospitalisation for heart failure
HLGT	High level group term
HLT	High level term
HNPCC	Hereditary non-polyposis colorectal cancer

HR	Hazard ratio
MACE	Major adverse cardiac event
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRHD	Maximum recommended human dose
mRNA	Messenger ribonucleic acid
N/A	Not applicable
NPY	Neuropeptide Y
OAD	Oral antidiabetic
PBRER	Periodic Benefit-Risk Evaluation Report
PG	Plasma glucose
P-gp	Phosphorylated glycoprotein
PSUR	Periodic Safety Update Report
PT	Preferred term
PY	Patient years
q.d.	*quaque die* (once daily)
RMP	Risk Management Plan
SAE	Serious adverse event
SCAR	Severe cutaneous adverse reaction
SDF-1α	Stromal derived factor type 1
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
SU	Sulfonylurea
TGFß	Transforming growth factor beta
TS	Treated set
TTO	Time to onset
T2DM	Type 2 diabetes mellitus
TZD	Thiazolidinediones
UACR	Urine albumin-to-creatinine ratio
US	United States
vs.	Versus

MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

There are no important identified or potential risks or missing information for Trajenta or Jentadueto.

SVIII.1 REFERENCES

Not applicable

ABBREVIATIONS

Not applicable

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

There are no safety concerns for Trajenta or Jentadueto and therefore no associated pharmacovigilance activities other than routine pharmacovigilance activities.

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

This part is not applicable as there are no planned or ongoing post-authorisation efficacy studies imposed for Trajenta or Jentadueto.

PART V RISK MINIMISATION MEASURES

RISK MINIMISATION PLAN

There are no important identified or potential risks or missing information topics for Trajenta or Jentadueto.

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR TRAJENTA AND JENTADUETO (LINAGLIPTIN AND LINAGLIPTIN / METFORMIN)

This is a summary of the Risk Management Plan (RMP) for Trajenta and Jentadueto. There are no important risks or missing information topics for Trajenta or Jentadueto.

The Summaries of Product Characteristics (SmPCs) for Trajenta and Jentadueto and their package leaflets give essential information to healthcare professionals and patients on how Trajenta and Jentadueto should be used.

This summary of the RMP for Trajenta and Jentadueto should be read in the context of all the information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns will be included in updates of the Trajenta and Jentadueto RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Trajenta and Jentadueto are authorised for Type 2 diabetes mellitus (see SmPCs for the full indications). Both medicines contain linagliptin as the active substance and in addition, Jentadueto contains metformin. Both Trajenta and Jentadueto are given orally.

Further information about the evaluation of benefits of these medicines can be found in the EPARs for Trajenta and Jentadueto, including plain-language summaries, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

There are no important risks or missing information topics for Trajenta or Jentadueto.

ABBREVIATIONS

EMA	European Medicines Agency
EPAR	European Public Assessment Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
T2DM	Type 2 diabetes mellitus

PART VII APPENDICES

PART VII TABLE OF CONTENTS

APPENDIX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

There are no specific adverse event follow-up forms for Trajenta or Jentadueto.

APPENDIX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

There are no additional risk minimisation activities for Trajenta or Jentadueto.