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EU Risk Management Plan for Trajenta (linagliptin) and Jentadueto (linagliptin+metformin)

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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.

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	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

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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

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PART II SAFETY SPECIFICATION

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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.

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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.

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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

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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.

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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.

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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]

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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].

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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.

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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].

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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]

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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

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  - 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

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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

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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.

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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].

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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 Cmax) were free

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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.

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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.

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R10-5403 Matveyenko AV, Dry S, Cox HI, Moshtaghian A, Gurlo T, Galasso R, et al. Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes: interactions with metformin. Diabetes 2009;58:1604-1615

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SII.2.2 Unpublished references

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U10-1492	BI 1356 BS (linagliptin) and Metformin: 13-week oral (gavage) combination toxicity study in rats. 09B104. 12 Oct 2010
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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

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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.

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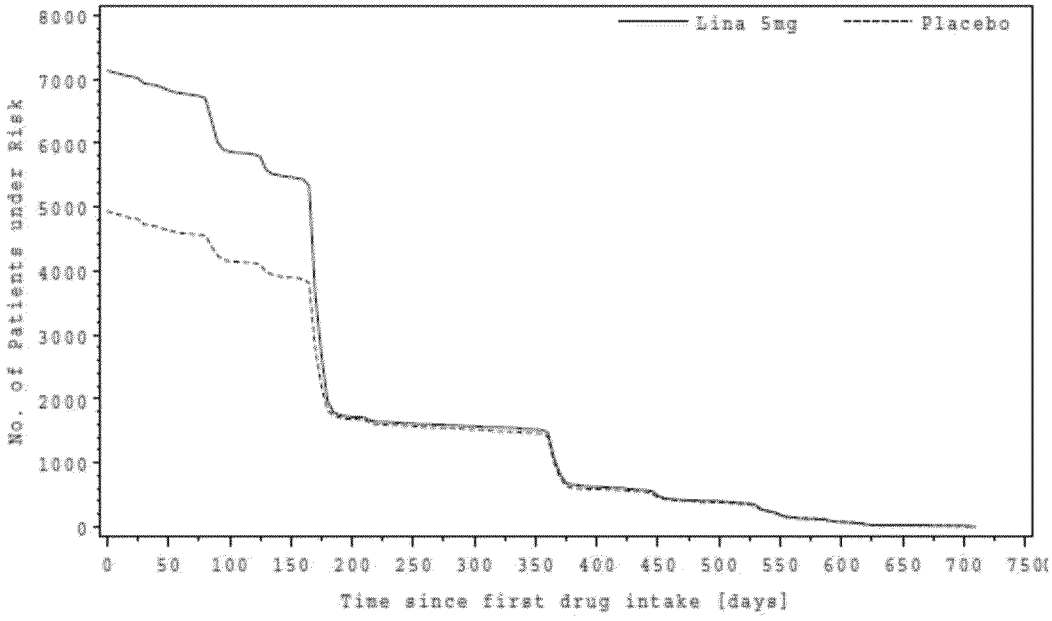
SIII.1 RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES WITH LINAGLIPTIN 5 MG IN PATIENTS WITH T2DM (SAF-2)

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

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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.

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

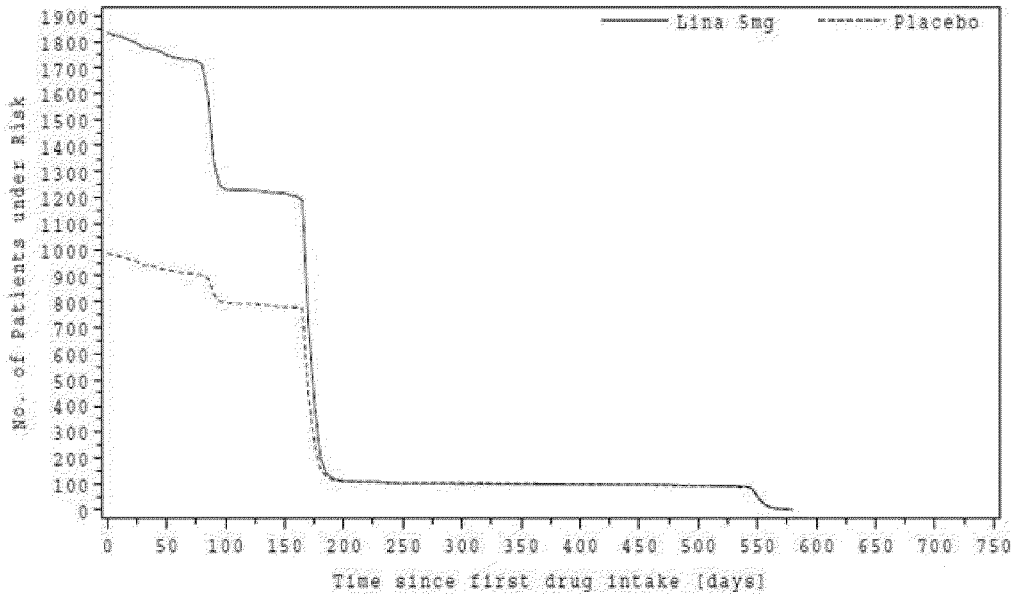
Race	Placebo		Linagliptin	
	Number of patients, N (%)	Patient-time [years]	Number of patients, N (%)	Patient-time [years]
White	2852 (57.8)	1952.3	4060 (56.9)	2488.8
Black	306 (6.2)	176.7	303 (4.2)	175.9
Asian	1778 (36.0)	1004.4	2773 (38.9)	1406.4
Total	4936 (100.0)	3133.4	7136 (100.0)	4071.1

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	1332	1217	112	101	100	99	97	97	94	51

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

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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

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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)

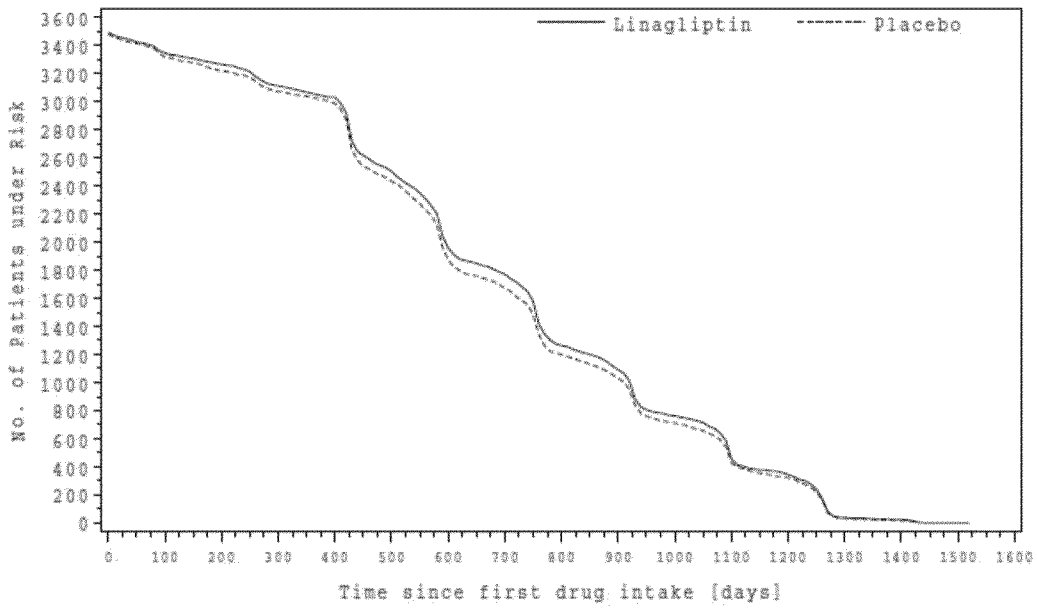
	Placebo + Metformin		Linagliptin + Metformin	
	Number of patients, N (%)	Patient-time [years]	Number of patients, N (%)	Patient-time [years]
Race, N (%)				
White	443 (44.9)	235.0	958 (52.2)	409.2
Black	5 (0.5)	2.9	11 (0.6)	5.5
Asian	538 (54.6)	271.8	866 (47.2)	393.3
Total	986 (100.0)	509.7	1835 (100.0)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

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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

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SIII.Table 10 Exposure by race (1218.22)

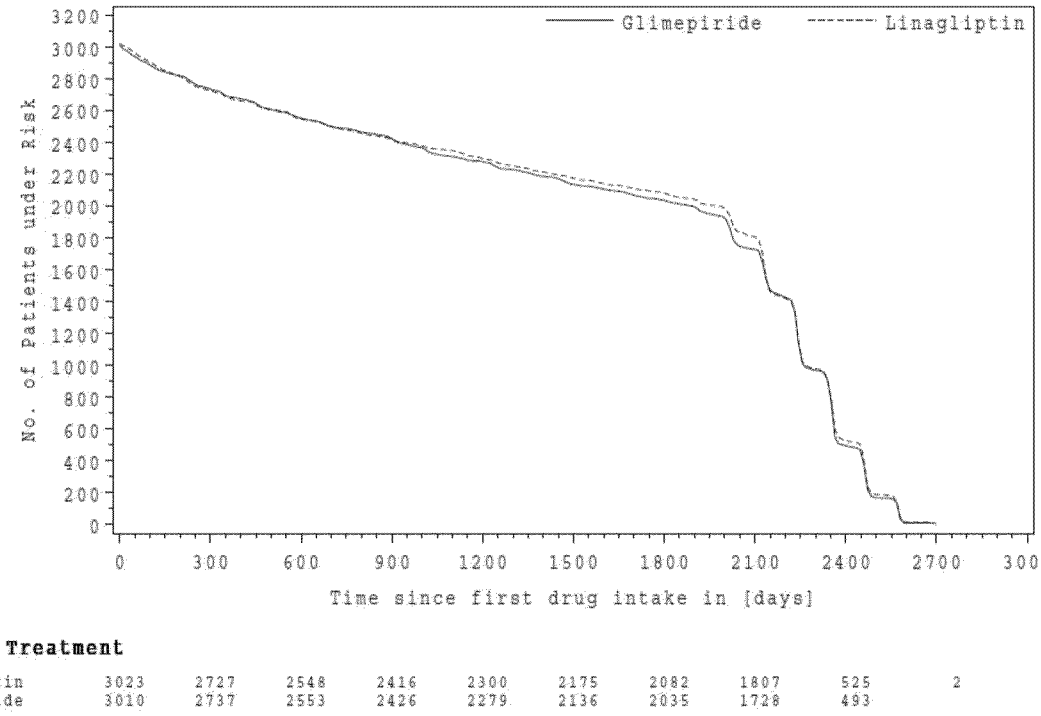
	Placebo		Linagliptin	
Race	**Number of patients, N (%)**	**Patient-time [years]**	**Number of patients, N (%)**	**Patient-time [years]**
White	2679 (79.5)	5249.6	2827 (80.9)	5469.7
Black	217 (6.2)	368.5	194 (5.6)	340.6
Asian	499 (14.3)	967.8	473 (13.5)	955.9
Total	3485 (100.0)	6585.9	3494 (100.0)	6766.2

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

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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.

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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

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

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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?	Yes
Rationale	Not applicable

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.

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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.

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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, 13 female patients became pregnant during clinical trials with linagliptin, linagliptin/metformin, or linagliptin/empagliflozin. Additionally, 2 cases have been reported from observational studies, and 21 cases from spontaneous sources, for a total of 36 cases of drug exposure during pregnancy from all sources.	-
Breastfeeding women	Not included in the clinical trial programme	Not applicable
Patients with relevant co-morbidities		
• Patients with severe hepatic impairment	Trial 1218.27 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 1218.26 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 1218.43 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 1218.64 113 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).	--

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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 1218.22 (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 1218.74 (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 cardiovascular impairment	Meta-analysis In a prospective meta-analysis of independently adjudicated CV events from 19 Phase III clinical studies involving 9459 patients with T2DM, linagliptin treatment was not associated with an increase in CV risk. This included patients with a known history of coronary artery disease and cerebrovascular disease.	4421.3 PY

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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 cardiovascular impairment (cont'd)	Trial 1218.22 (CARMELINA) . In this trial, 3494 patients, all with CV impairment, were treated with linagliptin 5 mg. Trial 1218.74 (CAROLINA) In this trial, 2794 patients with CV impairment (e.g. those with CV risk factors A [pre-existing vascular disease], B [evidence of vascular-related end-organ damage], or D [2 or more specified CV risk factors – hypertension, smoking, dyslipidaemia, T2DM ≥10 years]) were treated with linagliptin 5 mg.	
• 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 1218.22 and 1218.74, respectively.	--
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical trial programme	Not applicable

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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
Other		
• Paediatric patients	To date, linagliptin has been investigated in a phase 2 randomised, double-blind, placebo-controlled paediatric dose-finding study (1218.56) of 1 mg and 5 mg linagliptin in 39 children and adolescents from 10-17 years of age with T2DM. A paediatric development programme including subjects from 10 to 17 years of age has been agreed upon by the EMA (P/114/2009). As part of the PIP, 1218-0091 (DINAMO), 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 was initiated in March 2018. Treatment of children and adolescents with linagliptin is currently not recommended.	--
• Elderly patients (>80 years)	Elderly patients were included in the clinical trials. However, prior to the CV safety studies 1218.22 (now complete) and 1218.74 (ongoing), linagliptin had not been investigated in patients >80 years.	
	Trial 1218.22 (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.	1218.22: Lina: 406.5 PY
	Trial 1218.74 (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.	1218.74: Lina: 380.8 PY

Data source: Trajenta/Jentadueto PBRER (reporting interval 03 May 2015 to 02 May 2018) [s00067010-01], 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, 1218.26 [U10-1467-02], 1218.43 [U11-3170-01], 1218.56 [c02827550-02], 1218.64 [U13-1283-01], 8-05-output-rmp-carmelina-2018-06-11 [data on file] tables 1.3 and 1.5, 1218.22 [c22196815-02], 1218.74 [c23238241-01] xlinarmp—08—study-report-body [data on file], tables 1.3 and 1.5

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SIV.4 REFERENCES

SIV.4.1 Published references

Not applicable.

SIV.4.2 Unpublished references

c02827550-02 A randomised, double-blind, placebo-controlled parallel group dose-finding study of linagliptin (1 mg or 5 mg administered orally once daily) over 12 weeks in children and adolescents, from 10 to 17 years of age, with type 2 diabetes mellitus. 1218.56. 14 Dec 2017.

c22196815-02 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. 1218.22. 03 Aug 2018.

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. 1218.74. Mar 2019.

s00016631-17 Risk Management Plan for Linagliptin Type 2 diabetes mellitus, Version 11.0. 30 Mar 2017.

s00067010-01 Periodic Benefit-Risk Evaluation Report for Linagliptin (Trajenta) and Linagliptin + Metformin (Jentadueto), Reporting Period from 03 May 2015 to 02 May 2018. 10 Jul 2018.

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. 1218.26. 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. 1218.43. 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. 1218.64. 04 Mar 2013.

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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

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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 13 723 542 PY for the time period 02 May 2011 (international birthdate) to 30 Apr 2019.

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 2019

Region / country	Cumulative exposure [PY]
EEA	2 227 177
EU countries	[redacted]
Austria	
Belgium	
Bulgaria	
Croatia	
Republic of Cyprus	
Czech Republic	
Denmark	
Estonia	
Finland	
France	

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SV.Table 1 (cont'd) Cumulative exposure from marketing experience by region for Trajenta up to 30 Apr 2019

Region / country	Cumulative exposure [PY]
Germany	[redacted]
Greece	
Hungary	
Ireland	
Italy	
Latvia	
Lithuania	
Luxembourg	
Malta	
Netherlands	
Poland	
Portugal	
Romania	
Slovak Republic	
Slovenia	
Spain	
Sweden	
UK	
US and Canada	2 224 398
Japan	[redacted]
Other	6 026 422
Total	**13 723 542**

Data source: data on file, EA-008 Trajenta exposure (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 3 007 529 PY for the time period 01 Feb 2012 (international birthdate) to 30 Apr 2019.

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

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SV.Table 2 Cumulative exposure from marketing experience by region for Jentadueto up to 30 Apr 2019

Region / country	Cumulative exposure [PY]
EEA	630 344
EU countries	
Austria	[redacted]
Belgium	
Bulgaria	
Croatia	
Republic of Cyprus	
Czech Republic	
Denmark	
Estonia	
Finland	
France	
Germany	
Greece	
Hungary	
Ireland	
Italy	
Latvia	
Lithuania	
Luxembourg	
Malta	
Netherlands	
Poland	
Portugal	
Romania	
Slovak Republic	
Slovenia	
Spain	
Sweden	
UK	

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SV.Table 2 (cont'd) Cumulative exposure from marketing experience by region for Jentadueto up to 30 Apr 2019

Region / country	Cumulative exposure [PY]
US and Canada	351 452
Japan	--
Other	2 025 733
Total	**3 007 529**

Data source: data on file, EA-022 Jentadueto exposure (2019 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

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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.

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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.

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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

This RMP update was prompted by the completion of the CAROLINA trial (1218.74) [c23238241-01], a phase III multicentre, multinational, randomised, double-blind, parallel group, comparator-controlled trial of linagliptin versus glimepiride designed to evaluate the long-term CV safety in T2DM patients at increased cardiovascular risk, a population frequently encountered in clinical practice. Patients were predominantly treated with metformin background therapy (83.2% of study population). The trial was included as a category 3 pharmacovigilance activity in the RMP.

CAROLINA (1218.74)
6033 patients, all at increased risk for CV events, were randomised and included in the TS in this multinational trial, conducted in 607 sites in 43 countries worldwide. Of these, 6014 patients were analysed in the TS_D set that excluded 19 patients (see Section SVII.3.1 for details on the composition of the analysis sets). In the TS, 3023 patients were treated with linagliptin and 3010 patients with glimepiride and in the TS_D, 3014 patients were treated with linagliptin and 3000 patients with glimepiride.

The study was set up with prospective centralised blinded adjudication of all cardio/cerebrovascular trigger events through an independent, blinded, external CEC. Additionally, a separate independent, blinded, external CEC was established for adjudication

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of pancreatic events. There was also an Oncology Assessment Committee for detailed assessment of patients with solid malignancies as defined in the Oncology Assessment Committee charter. The median time in trial was 6.3 years in both treatment groups and the median exposure to trial medication was 5.9 years in both treatment groups.

The CAROLINA trial demonstrated non-inferiority of linagliptin to glimepiride for time to first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (3-point MACE) in patients with T2DM at elevated CV risk and on stable glucose-lowering therapy (predominately metformin (83.2%)) and usual care for CV disease, Superiority of linagliptin over glimepiride was not achieved for the 3-point MACE endpoint. Similarly, no treatment difference was observed for the time to first 4-point MACE (hospitalisation for unstable angina pectoris in addition to 3-point MACE components).

Further analyses showed no significant treatment differences for all-cause mortality, CV death, and non-CV death (linagliptin) or for heart failure outcomes including hospitalisation for heart failure alone, or when analysed combined with CV death. Similarly, there was no significant treatment difference for investigator-reported heart failure AEs.

The frequency of patients with AEs was similar in the linagliptin treatment group and in the glimepiride group. Frequencies for most AE categories were also comparable. The proportion of patients with AEs assessed as being drug related by the investigator was lower in the linagliptin treatment group than in the glimepiride group. This difference was mainly driven by the PT hypoglycaemia that was more frequently reported for patients treated with glimepiride.

The frequency of patients with hypoglycaemia AEs was substantially lower in the linagliptin group compared with glimepiride. This was consistently observed across all hypoglycaemia categories (any hypoglycaemia, moderate/severe hypoglycaemia, clinically important hypoglycaemia defined by PG<54 mg/dL and severe hypoglycaemia defined as requiring assistance).

There was no meaningful imbalance between treatment groups in the number of patients with any of the protocol-predefined AESIs, which were hypersensitivity reactions, skin lesions, hepatic events, renal events, pancreatitis, and pancreatic cancer. There were also no relevant differences between the 2 groups for further AEs examined, including malignancies, immunological reactions, angioedema, arthralgia, and bullous conditions.

The PT pemphigoid (as part of bullous conditions) was reported for 5 patients (serious in 3 patients) in the linagliptin group and none of the patients in the glimepiride group.

The overall frequency of CECP-confirmed pancreatic cancer was low with 16 patients (0.5%) in the linagliptin group and 24 patients (0.8%) in the glimepiride group.

The safety profile of linagliptin in this trial population was consistent with the known safety profile of the drug.

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CARMELINA (1218.22)
6979 patients, all with a high risk of CV events, were treated in this multinational trial, conducted in 660 centres in 27 countries worldwide. Most patients (74%) had prevalent kidney disease at baseline, defined as eGFR <60 mL/min/1.73m^2 or UACR ≥300mg/g, and 57% of patients had both established macrovascular disease and albuminuria. Approximately 71% of the patient population were considered to be at high risk or very high risk for adverse kidney events on the basis of their eGFR and albuminuria status. The study was set up with prospective centralised blinded adjudication of all cardio/cerebrovascular trigger events through an independent, blinded, external CEC. Additionally, separate independent, blinded, external CECs were established for adjudication of renal and pancreatic events. There was also an Oncology Assessment Committee for causality assessment of solid cancers with trial medication. The median time in this trial was 2.2 years in both the linagliptin and placebo groups, and the median treatment exposure was 1.9 and 1.8 years in the linagliptin and placebo groups, respectively.

The study included 3494 patients treated with linagliptin (5 mg) and 3485 patients treated with placebo. Both treatments were added to standard of care targeting regional standards for HbA_{1c} and CV risk factors. At baseline, 57% of patients were treated with insulin, 54% with metformin, and 32% with a sulfonylurea. The overall incidence of AEs and SAEs in patients receiving linagliptin was similar to that in patients receiving placebo. Safety data from this study was in line with previous known safety profile of linagliptin. When added to standard of care, linagliptin did not increase the risk of MACE events overall or in subgroups based on HbA_{1c}. Renal outcome events were comparable between linagliptin and placebo-treated patients overall as well as in subgroups such as eGFR. There was no increased risk in hospitalisation for heart failure which was an additional adjudicated endpoint, compared to standard of care without linagliptin in patients with T2DM.

In the treated population, severe hypoglycaemic events (requiring assistance) were reported in 3.0% of patients on linagliptin and in 3.1% on placebo. Among patients who were using sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2.0% in linagliptin-treated patients and 1.7% in placebo-treated patients. Among patients who were using insulin at baseline, the incidence of severe hypoglycaemia was 4.4% in linagliptin-treated patients and 4.9% in placebo treated patients.

During the entire observation period in the study, 9 patients (0.3%) in the linagliptin group were confirmed by the adjudication committee with acute pancreatitis vs. 5 patients (0.1%) in the placebo group.

7 cases (0.2%) of pemphigoid as a PT were observed in the linagliptin group and none in the placebo group.

There were 15 cases of pancreatic cancer confirmed by the adjudication committee during the entire study observation period; 11 (0.3%) of which were reported in the linagliptin treated group and 4 (0.1%) of which were reported in the placebo treated group.

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In addition to the safety pool of 12 072 patients from randomised, double-blind, placebo-controlled studies (SAF-2), the 6979 treated patients from CARMELINA and 6033 treated patients from the CAROLINA study add considerably to the body of information concerning important risks and missing information for Trajenta. Based on the cumulative information gathered from non-clinical, clinical, and post-marketing sources, and augmented by data from the CARMELINA and CAROLINA studies, the following changes to the safety concerns are proposed in this RMP:

Important identified risks
Removal of the following topics as important identified risks:

- Hypoglycaemia
- Lactic acidosis

Hypoglycaemia
Due to its mechanism of action, linagliptin bears little risk of hypoglycaemia, also when taken in addition to metformin. In trial 1218.18, where linagliptin or placebo were added to a background therapy of metformin + SU, the risk of hypoglycaemia was increased in the linagliptin group (22.7%) compared to placebo (14.8%). The logistic regression of the occurrence of any hypoglycaemic events indicated an odds ratio of 1.644 (95% CI: 1.14 to 2.38, p = 0.0083), i.e. an increased probability of hypoglycaemic events with linagliptin treatment [U09-2458-02]. This increased risk for hypoglycaemia has not been observed in analyses of linagliptin as monotherapy or in combination with insulin or other antidiabetic medications except SUs.

In the SAF-2 dataset of randomised, double-blind, placebo-controlled studies of linagliptin in patients with T2DM, hypoglycaemia occurred at similar frequencies (approximately 9%) in the linagliptin and placebo treatment arms. The incidence rate ratio (1.14; 95% CI 1.0,1.3) and incidence risk ratio (1.11; 95% CI 1.0,1.2) for linagliptin vs. placebo showed no substantial differences between treatment groups. Characteristics of hypoglycaemia AEs such as seriousness, outcome, and intensity were also balanced between the treatment groups (data source: data on file, 8-05-output-rmp-2017-final, Table 7.2.1).

Trial 1218.22 (CARMELINA)
Similar results were seen in CARMELINA, the placebo-controlled CV outcome trial where the frequencies of patients with investigator-defined hypoglycaemia were comparable between treatment groups (linagliptin 29.7%, placebo 29.4%), with incidence rate and incidence risk ratios for linagliptin vs. placebo showing no substantial differences between the groups (SVII.Table 3). Hypoglycaemic AEs with PG <54 mg/dL or any severe hypoglycaemic event (i.e. one requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions) were also balanced between treatment groups (linagliptin 15.9%, placebo 16.4%) (data source, data on file 1218.22 CTR [c22196815-02], Table 12.1.4: 1).

In CARMELINA, 97.4% of treated patients were using at least 1 antidiabetic medication at baseline with the most frequent being insulin and analogues (57.3%), metformin (54.0%), and sulfonylureas (31.9%). Overall, the number of patients with serious events was low (<4%).

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There was 1 fatal event in the linagliptin treatment arm unrelated to linagliptin use but due to underlying insulin pump failure. The intensities of most hypoglycaemia events were mild to moderate and similar between the treatment groups; this was also the case for severe events. The vast majority of patients had recovered from the hypoglycaemia at the time of database lock. Further details are given in SVII.Table 3.

Subgroup analyses by baseline use of insulin (+/- OAD) revealed similar rates of hypoglycaemia in SAF-2 (47.6/100PY vs. 49.1/100PY for placebo and linagliptin, respectively). For patients receiving insulin at baseline in CARMELINA, rates were numerically lower in the linagliptin group than the placebo group for both overall hypoglycaemic AEs (36.8% vs. 38.2% for linagliptin and placebo, respectively) and for hypoglycaemic AEs with PG <54 mg/dL (22.4% vs. 24.4% for linagliptin and placebo, respectively). The frequency of severe hypoglycaemic AEs was balanced between the treatment groups (linagliptin: 4.4%, placebo: 4.9%) for patients receiving insulin at baseline.

Subgroup analyses by insulin background were not possible in CAROLINA as subjects with insulin use at baseline were excluded from the study.

In CARMELINA no clinically meaningful differences in hypoglycaemia between treatment groups were shown with regard to other subgroups including gender, age, or renal impairment (Data on file: data source, 8-05-output-rmp-carmelina-2018-06-25, Tables 2.1.1.6 to 2.1.1.9).

For patients who were receiving SUs at baseline in CARMELINA, the frequency of any confirmed hypoglycaemic AE was numerically higher in the linagliptin group compared with placebo (24.9% and 21.7%, respectively). A similar pattern was observed for any hypoglycaemic AE with PG <54 mg/dL or any severe hypoglycaemic AE (linagliptin: 12.2%, placebo: 9.7%). The frequency of severe hypoglycaemic AEs was balanced between the treatment groups (linagliptin: 2.0%, placebo: 1.7%). For patients who were not receiving SU at baseline, the frequency of these events was numerically lower in the linagliptin group vs. placebo (Table 15.3.1.6.13). (Data source, 1218.22 CTR [c22196815-02], Table 15.3.1.6.13).

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SVII.Table 3 Overview on hypoglycaemia (TS – 1218.22)

	Placebo	Linagliptin
Number of patients treated, N (%)	3485 (100.0)	3494 (100.0)
Total overall time at risk (PY)	5075.6	5214.6
Patients with hypoglycaemia, N (%)	1024 (29.4)	1036 (29.7)
95% CI	[27.9, 30.9]	[28.2, 31.2]
Rate/100 PY	20.17	19.87
Incidence rate ratio[1], (95% CI)	0.98 [0.90, 1.07]	
Incidence risk ratio[1], (95% CI)	1.01 [0.94, 1.09]	
Seriousness[2,3], N (%)	39 (3.8)	30 (2.9)
Resulted in Death	0 (0.0)	1 (0.1)
Immediately life threatening	5 (0.5)	8 (0.8)
Disability	1 (0.1)	1 (0.1)
Requires hospitalisation	26 (2.5)	17 (1.6)
Prolongs hospitalisation	1 (0.1)	2 (0.2)
Congenital Anomaly or Birth Defect	0 (0.0)	0 (0.0)
Other Medically Important Serious Event	6 (0.6)	6 (0.6)
Outcome[2,4], N (%)	1024 (100.0)	1036 (100.0)
Recovered	1014 (99.0)	1024 (98.8)
Not yet recovered	7 (0.7)	8 (0.8)
Sequelae	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	1 (0.1)
Unknown	3 (0.3)	3 (0.3)
Intensity[2], N (%)	1021 (99.7)	1032 (99.6)
Mild	745 (72.8)	744 (71.8)
Moderate	199 (19.4)	206 (19.9)
Severe	77 (7.5)	82 (7.9)

[1]Ratio linagliptin vs. placebo

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

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

[4]Each of the outcomes could be individually assigned to an event, i.e. fatal would not be a subset of not recovered

Data source: data on file, 8-05-output-rmp-carmelina-2018-06-25, Table 5.1.1

Trial 1218.74 (CAROLINA)

Results from the recently completed CAROLINA trial, comparing linagliptin to glimepiride were in line with those seen in CARMELINA. In this trial, 89.9% of treated patients were using at least 1 antidiabetic medication at screening, most commonly metformin (83.2%) and SU (28.4%) (data source: 1218.74 CTR [c23238241-01], Tables 10.4.3: 1 and 15.1.4.2: 3).

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As shown in SVII.Table 4, the frequency of patients with investigator-defined hypoglycaemia was markedly lower in the linagliptin group than in the glimepiride group (10.6% vs. 37.7%, respectively). This difference was consistent for all analysed characteristics of the hypoglycaemic events including clinically important hypoglycaemia (PG <54 mg/dL) or severe (requiring assistance) hypoglycaemia.

Subgroup analyses with respect to eGFR categories showed a trend for a higher frequency of investigator-defined hypoglycaemic AEs in both treatment groups by worsening of renal function, i.e. lower eGFR value categories. As for the overall population, the frequencies of hypoglycaemic AEs were lower in the linagliptin group than in the glimepiride group within each eGFR subgroup category showing a consistent treatment effect across subgroups. Prior use of SU or glinide also had no obvious effect on the treatment effect. The pronounced treatment effect on investigator-defined hypoglycaemic AEs (lower frequencies in the linagliptin group than in the glimepiride group) was also consistent across the other analysed subgroups.

Few patients were hospitalised due to investigator-defined hypoglycaemia, but significantly less frequently in the linagliptin group (2 patients, 0.1%) compared with the glimepiride group (27 patients, 0.9%). The OR was 0.07 (95% CI 0.02, 0.31).There were no fatal events of hypoglycaemia in this trial (data source, 1218.74 CTR [c23238241-01], Table 11.1.2.4.4: 2).

SVII.Table 4 Patients with investigator-defined hypoglycaemic adverse events by treatment and characteristics of hypoglycaemic events – TS_D+7

	Glimepiride N (%)	Linagliptin N (%)
Number of patients	3000 (100.0)	3014 (100.0)
Patients with any investigator-defined hypoglycaemic AE	1132 (37.7)	320 (10.6)
PG ≤70 mg/dL or severe[1] (= confirmed)[2]	1041 (34.7)	257 (8.5)
PG <54 mg/dL or severe[1]	523 (17.4)	94 (3.1)
Any severe[1]	65 (2.2)	10 (0.3)

[1] Severe hypoglycaemic AE: hypoglycaemic event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

[2] Confirmed hypoglycaemic AE: investigator defined hypoglycaemic AE confirmed by PG ≤70 mg/dL or any severe hypoglycaemic AE.

Data source: 1218.74 CTR [c23238241-01], Table 12.1.3: 1

Conclusion

The placebo-controlled pooled clinical trial dataset (SAF-2) and results from the CV outcome trials were not suggestive of any increased risk of hypoglycaemia with linagliptin when used as monotherapy or in combination with antidiabetic medications other than SUs. In the SAF-2 dataset and in the CARMELINA trial, hypoglycaemia was reported at comparable rates between the linagliptin and placebo groups. Event characteristics, such as seriousness, outcome and intensity were similar between the 2 treatment groups.

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There was also no increased risk of hypoglycaemia when analysed by baseline use of insulin. Hypoglycaemia rates in SAF-2 were comparable when analysed by background use of insulin (+/- OAD) and numerically lower in the linagliptin group compared with the placebo group in CARMELINA. Subgroup analyses by insulin background were not possible in CAROLINA as subjects with insulin use at baseline were excluded from the study.

It is well known that SUs increase the risk of hypoglycaemia (relative risk estimates between 3 and 7 when comparing SU monotherapy with metformin, TZDs, or DPP-4 inhibitors) [R12-2825], and this was the case with the clinical trials of linagliptin, where an increased risk for hypoglycaemia was observed only when linagliptin was administered on a background of metformin + SU (35.5/100 PY vs. 60.1/100 PY for the placebo and linagliptin groups, respectively in SAF-2). In the CAROLINA trial, hypoglycaemia, was reported much more frequently with the active comparator glimepiride than with linagliptin. This was also true for clinically important hypoglycaemia (plasma glucose <54 mg/dL) or severe hypoglycaemia which was substantially lower in the linagliptin group (3.1%) compared with the glimepiride group (17.4%) and for severe hypoglycaemia alone (0.3% vs. 2.2%, for linagliptin vs. glimepiride, respectively).

As routine risk minimisation measures (including the SmPC) are considered sufficient, and considering that no further characterisation of hypoglycaemia is planned or needed, BI proposes to remove hypoglycaemia as an important identified risk from the RMP based on the GVP module V revision 2 guidance.

Lactic acidosis (Jentadueto only)
No case of lactic acidosis was reported in the SEA-2 safety pool of clinical trials with linagliptin + metformin (Data on file: data source, 8-05-output-rmp-2017-final, tables 7.3.12 and 4.2.12.1).

3 cases of lactic acidosis, 2 in the linagliptin group and 1 in the placebo group were reported by patients on background metformin in CARMELINA (Data on file: data source, 8-05-output-rmp-carmelina-2018-06-25, Table 5.2.1).

3 cases of lactic acidosis, 2 in the linagliptin group and 1 in the glimepiride group were reported by patients on background metformin in CAROLINA. 2 (1 in each treatment group) of the 3 lactic acidosis events were serious and the patients recovered in all 3 cases. In the linagliptin group, the cases were mild and severe in intensity and the case in the glimepiride group was of moderate intensity (data source: data on file, xlinarmp--8—study-report-body, Table 5.2.1).

Conclusion
Very few events of lactic acidosis have been reported in clinical trials with linagliptin+metformin. Routine risk minimisation measures (including the SmPC) are considered sufficient to mitigate this established and well-characterised risk with metformin and no further pharmacovigilance activities are planned. Therefore, BI proposes to remove lactic acidosis as an important identified risk for Jentadueto. Nevertheless, lactic acidosis will

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continue to be monitored through BI routine pharmacovigilance activities with updates presented in the PBRER in accordance with CHMP request.

Important potential risks
Removal of the following topics as important potential risks:

- Worsening of renal function
- Arthralgia
- Cardiac failure

Worsening of renal function
Worsening of renal function was identified as an important potential risk for linagliptin based on post-marketing reports of worsening of renal function that had been reported for another DPP-4 inhibitor (sitagliptin, Januvia [R11-2681]) and the fact that, in non-clinical data, linagliptin was found to be bound to DPP-4 in kidney tissue [U09-1028-01].

Worsening of renal function was added as an important potential risk to the RMP based on EMA request.

In addition to the analyses on MedDRA PT level, renal safety laboratory (including eGFR, and albumin creatinine ratio) were actively monitored during the long-term cardiovascular safety study CAROLINA (1218.74) [c23238241-01].

In randomised, placebo-controlled, clinical trials the incidence of worsening of renal function, was lower for linagliptin than placebo groups.

Clinical trial data
Patients with worsening of renal function were identified using the narrow SMQ 'acute renal failure' (20000003). In the CARMELINA trial, renal events 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 type 2 diabetes mellitus (SAF-2)

SVII.Table 5 provides an overview on worsening of renal function (SAF-2). AEs associated with worsening of renal function occurred more often under placebo than with linagliptin. The proportion of serious events and the intensity of the AEs were similar between both groups. AEs with the outcome "recovered" were reported more often in the linagliptin arm than under placebo treatment. There was 1 fatal AE in the placebo treatment arm.

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SVII.Table 5 Overview on worsening of renal function (SAF-2)

	Placebo	Linagliptin
Number of patients treated, N (%)	4936 (100.0)	7136 (100.0)
Total overall time at risk (PY)	3206.14	4162.28
Patients with worsening of renal function, N (%)	30 (0.6)	34 (0.5)
95% CI	[0.4, 0.9]	[0.3, 0.7]
Rate/100 PY	0.94	0.82
Incidence rate ratio[1] (95% CI)	1.03 [0.6, 1.7]	
Incidence risk ratio[1] (95% CI)	1.03 [0.6, 1.6]	
Seriousness[2,3], N (%)	12 (40.0)	14 (41.2)
Fatal	1 (3.3)	0
Disability/incapability	0	1 (2.9)
Required hospitalisation	7 (23.3)	9 (26.5)
Prolonged hospitalisation	2 (6.7)	4 (11.8)
Other	2 (6.7)	1 (2.9)
Outcome[2,4], N (%)		
Recovered	12 (40.0)	19 (55.9)
Not yet recovered	13 (43.3)	11 (32.4)
Sequelae	2 (6.7)	4 (11.8)
Fatal	1 (3.3)	0
Unknown	2 (6.7)	0
Intensity[2], N (%)		
Mild	10 (33.3)	13 (38.2)
Moderate	14 (46.7)	14 (41.2)
Severe	6 (20.0)	7 (20.6)

[1]Ratio linagliptin vs. placebo

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

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

[4]Each of the outcomes could be individually assigned to an event, i.e. fatal would not be a subset of not recovered.

Data source: data on file, 8-05-output-rmp-2017-final, Table 7.2.11

Trial 1218.22 (CARMELINA)

Composite renal endpoint data

The time to first occurrence of any of the following adjudication-confirmed renal endpoints was the key secondary endpoint in CARMELINA: renal death, sustained ESRD, sustained decrease of 40% or more in eGFR.

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A total of 633 patients were reported with an adjudication-confirmed key secondary endpoint event (first occurrence of any of the following adjudication-confirmed components: renal death, sustained ESRD or sustained decrease of 40% or more in eGFR from baseline [composite renal endpoint 1]). There were 327 patients (9.4%) with an event in the linagliptin group and 306 patients (8.8%) in the placebo group. The HR based on Cox regression for linagliptin vs. placebo was 1.04 (96% CI 0.88, 1.23). Linagliptin was therefore found to be not superior to placebo. Despite the positive trend observed for the analyses of combined sustained ESRD or renal death (linagliptin: 136 patients [3.9%], placebo: 154 patients [4.4%] with an event), the HR of 0.87 was not statistically significant (Data source, 1218.22 CTR [c22196815-02], tables 11.1.2.1: 1 and 11.1.3.7.1: 2).

Subgroup by eGFR

Subgroup analyses for the occurrence of the renal composite endpoint 1 (renal death, sustained ESRD or sustained decrease of 40% or more in eGFR from baseline) showed some fluctuation across eGFR categories but no evidence that treatment with linagliptin increased the risk for any of the components of composite renal endpoint 1 with increasing eGFR. The difference in HR for the renal composite endpoint 1 by eGFR categories ≥60 ml/min/1.73 m^2 and <60 ml/min/1.73 m^2 was considered a chance finding driven by the low numbers of events in patients with less severe renal impairment and does not reflect a negative benefit-risk evaluation in patients with baseline eGFR ≥60 ml/min/1.73 m^2.

Safety data

The frequencies of subjects with worsening of renal function AEs, defined by the narrow SMQ 'acute renal failure' were higher in the placebo group (7.5%) than in the linagliptin group (6.9%). Correspondingly, in this study, subjects treated with linagliptin had slightly lower rate and risk ratios for worsening of renal function than those treated with placebo. The number of AEs indicative of worsening of renal function were serious (over 60% in each treatment group) and similar between the placebo and linagliptin groups. Of the 7 events reported with a fatal outcome in the linagliptin group, only 1 was adjudicated as renal death by an independent external adjudication committee. Both the fatal cases in placebo arm were adjudicated as renal death. About half of the subjects in each treatment group had recovered from the AE. The treatment groups were similar with respect to AE outcomes and intensities. Further details are provided in SVII.Table 6.

Subgroup analyses showed that worsening of renal function AEs was reported more frequently by Black subjects in either treatment group (linagliptin 16.0%, placebo 15.2%), than White (linagliptin 6.5%, placebo 7.3%) or Asian subjects (linagliptin 5.9%, placebo 4.8%). However, within each racial category, differences between treatment groups were minimal. No substantial differences were seen in subgroup analyses by age or gender. As expected, the frequency of subjects reporting worsening of renal function increased in parallel with increasing degree of impaired renal function at baseline; however, within each category of baseline renal impairment, the proportions of subjects reporting worsening of renal function were similar between the 2 treatment groups (Data source: data on file, 8-05-output-rmp-carmelina-2018-06-25, Tables 2.1.11.6 to 2.1.11.9).

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SVII.Table 6 Overview on worsening of renal function AEs (TS – 1218.22)

	Placebo	Linagliptin
Number of patients treated, N (%)	3485 (100.0)	3494 (100.0)
Total overall time at risk (PY)	6408.9	6608.2
Patients with worsening of renal function, N (%)	260 (7.5)	242 (6.9)
95% CI	[6.6, 8.4]	[6.1, 7.8]
Rate/100 PY	4.06	3.66
Incidence rate ratio[1] (95% CI)	0.90 [0.76, 1.08]	
Incidence risk ratio[1] (95% CI)	0.93 [0.78, 1.10]	
Seriousness[2,3], N (%)	164 (63.1)	151 (62.4)
Resulted in Death	2 (0.8)	7 (2.9)
Immediately life threatening	11 (4.2)	6 (2.5)
Disability	5 (1.9)	3 (1.2)
Required hospitalisation	104 (40.0)	96 (39.7)
Prolongs hospitalisation	26 (10.0)	19 (7.9)
Other Medically Important Serious Event	35 (13.5)	40 (16.5)
Outcome[2,4], N (%)	260 (100.0)	242 (100.0)
Recovered	151 (58.1)	126 (52.1)
Not yet recovered	78 (30.0)	76 (31.4)
Sequelae	7 (2.7)	7 (2.9)
Fatal	2 (0.8)	7 (2.9)
Unknown	22 (8.5)	26 (10.7)
Intensity[2], N (%)	260 (100.0)	242 (100.0)
Mild	48 (18.5)	50 (20.7)
Moderate	125 (48.1)	104 (43.0)
Severe	87 (33.5)	88 (36.4)

[1]Ratio linagliptin vs. placebo

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

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

[4]Each of the outcomes could be individually assigned to an event, i.e. fatal would not be a subset of not recovered

Data source: data on file: 8-05-output-rmp-carmelina-2018-06-25, Table 5.1.11

Trial 1218.74 (CAROLINA)

The frequencies of subjects with worsening of renal function AEs, defined by the narrow SMQ 'acute renal failure' were balanced between treatment groups (5.2% vs. 5.9% for glimepiride and linagliptin, respectively) with the 95% CIs of the incidence risk and incidence rate ratios containing 1. Other event characteristics such as seriousness, outcomes and intensities were also similar in both groups.

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Worsening of renal function was fatal in 10 patients, including 4 (2.6%) in the glimepiride group and 6 (3.4%) in the linagliptin group. Further details are provided in SVII.Table 7.

As might be expected, the incidence of AEs indicative of renal function impairment increased with age and degree of renal impairment at baseline; however, there were no substantial differences between treatment groups in renal function impairment for any of the subgroups analysed (Data source: data on file, xlinarmp—08—study-report-body, tables 2.1.11.6 to 2.1.11.9).

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SVII.Table 7 Overview on worsening of renal function AEs (TS_D – 1218.74)

	Glimepiride	Linagliptin
Number of patients treated, N (%)	3000 (100.0)	3014 (100.0)
Total overall time at risk (PY)	14 310.4	14 459.2
Patients with Worsening of renal function, risk rate N (%)	156 (5.2)	178 (5.9)
Risk rate [95% CI]	[4.5, 6.1]	[5.1, 6.8]
Incidence rate (/100 PY) [95% CI]	1.09 [0.93, 1.28]	1.23 [1.06, 1.43]
Incidence rate ratio* [95% CI]	1.13 [0.91, 1.40]	
Risk ratio* [95% CI]	1.14 [0.92, 1.40]	
Seriousness#, N (%)	64 (41.0)	73 (41.0)
Resulted in death	4 (2.6)	6 (3.4)
Immediately life threatening	3 (1.9)	2 (1.1)
Disability	0 (0.0)	1 (0.6)
Required hospitalisation	27 (17.3)	36 (20.2)
Prolonged hospitalisation	7 (4.5)	11 (6.2)
Other comparable medical criteria	28 (17.9)	26 (14.6)
Outcome#~, N (%)		
Recovered	71 (45.5)	82 (46.1)
Not yet recovered	68 (43.6)	77 (43.3)
Sequelae	3 (1.9)	7 (3.9)
Fatal	4 (2.6)	6 (3.4)
Unknown	10 (6.4)	6 (3.4)
Intensity#, N (%)		
Mild	60 (38.5)	68 (38.2)
Moderate	68 (43.6)	77 (43.3)
Severe	28 (17.9)	33 (18.5)

* Ratio Linagliptin vs. Glimepiride ("risk ratio" was previously referred to as "incidence risk ratio").
# Percentages are calculated using the number of all patients with Worsening of renal function as denominator.
%_Patients can be counted in more than 1 seriousness category.
~ Outcome categories are mutually exclusive.
Data source: xlinarmp—08—study-report-body, Table 5.1.11

Conclusion

In CARMELINA, no significant difference was shown between linagliptin and placebo in time to first occurrence of renal death, sustained ESRD or sustained decrease of 40% or more in eGFR from baseline (HR 1.04: 96% CI 0.88, 1.23). The results of this CV outcome trial which was conducted in a vulnerable population with a particularly high proportion of patients with prevalent kidney disease, confirmed the renal safety of treatment with linagliptin and reinforced findings from the SAF-2 pool of randomised, placebo-controlled

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clinical trials of linagliptin showing no difference between linagliptin and placebo in terms of renal safety. These results were further supported by the CAROLINA study which showed similar frequencies of renal events in the linagliptin and glimepiride treatment groups. As no safety concerns with respect to renal function have been shown from these clinical trials, and no further clinical data are expected, BI proposes to remove 'worsening of renal function' as an important potential risk for linagliptin.

Arthralgia
Arthralgia was defined as an important potential risk for patients receiving linagliptin monotherapy, based on a request of EMA following the review of the class of DPP-4 inhibitors.

Several hypotheses have emerged from pre-clinical studies that have suggested a possible role of DPP-4 inhibitors in joint disorders. These hypotheses vary from DPP-4 having an immunomodulatory effect on lymphocytes and fibroblasts to a direct involvement of GLP-1 in joint inflammation, the levels of which are elevated as a result of DPP-4 inhibition. However, conclusive evidence regarding the role of DPP-4 inhibition in causation of joint pathologies is lacking [R16-1052, P16-02691]. Joint or bone toxicity were not observed in any of the general toxicity studies with linagliptin.

Clinical trial data
Patients with arthralgia were identified using the primary path of the MedDRA HLGT 'joint disorders.' MedDRA version 20.1 was used in SAF-2 and CARMELINA and version 21.0 in CAROLINA.

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

SVII.Table 8 provides an overview on arthralgia (SAF-2) based on the HLGT 'joint disorders'. Arthralgia-related events occurred more often in the placebo group than in the linagliptin group in SAF-2. Correspondingly, the incidence risk ratio and incidence rate ratio favoured linagliptin. This was also the case for the PT 'arthralgia' which was reported by 126 patients (2.6%) in the placebo group compared 148 patients (2.1%) in the linagliptin group (Data source: data on file, 8-05-output-rmp-2017-final, Table 4.3.5.1). Event characteristics such as seriousness, reported outcomes and intensity were similar between the 2 treatment groups.

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SVII.Table 8 Overview on arthralgia (SAF-2)

	Placebo	Linagliptin
Number of patients treated, N (%)	4936 (100.0)	7136 (100.0)
Total overall time at risk (PY)	3091.46	4055.69
Patients with arthralgia, N (%)	232 (4.7)	281 (3.9)
95% CI	[4.1, 5.3]	[3.5, 4.4]
Rate/100 PY	7.50	6.93
Incidence rate ratio[1], (95% CI)	0.90 [0.8, 1.1]	
Incidence risk ratio[1], (95% CI)	0.92 [0.8, 1.1]	
Seriousness[2,3], N (%)	10 (4.3)	12 (4.3)
Required hospitalisation	10 (4.3)	12 (4.3)
Outcome[2,4], N (%)		
Recovered	124 (53.4)	142 (50.5)
Not yet recovered	105 (45.3)	137 (48.8)
Sequelae	3 (1.3)	1 (0.4)
Unknown	0	1 (0.4)
Intensity[2], N (%)		
Mild	141 (60.8)	171 (60.9)
Moderate	81 (34.9)	101 (35.9)
Severe	10 (4.3)	9 (3.2)

[1]Ratio linagliptin vs. placebo

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

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

[4]Each of the outcomes could be individually assigned to an event, i.e. fatal would not be a subset of not recovered

Data source: data on file, 8-05-output-rmp-2017-final, Table 7.2.5

Clinical trial data (Trial 1218.22 - CARMELINA)

As shown in SVII.Table 9, the incidence of arthralgia-related AEs was similar between treatment groups. Event characteristics such as seriousness, outcome and intensity were also similar between the treatment groups. 3 patients (0.1%) in the placebo group had arthralgia-related event leading to discontinuation from trial drug compared with none in the linagliptin group. Events coding to the PT 'arthralgia' were reported at comparable frequencies in the placebo (2.8%) and in the linagliptin groups (2.6%). Among serious arthralgia-related events, the PT 'arthralgia' was reported by only 1 subject in each treatment group (Data source: 1218.22 CTR [c22196815-02], Tables 15.3.1.8.13 and 15.3.1.8.14).

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SVII.Table 9 Overview on arthralgia (TS – 1218.22)

	Placebo	Linagliptin
Number of patients treated, N (%)	3485 (100.0)	3494 (100.0)
Total overall time at risk (PY)	6380.5	6533.1
Patients with arthralgia, N (%)	198 (5.7)	217 (6.2)
95% CI	[5.0, 6.5]	[5.5, 7.1]
Rate/100 PY	3.10	3.32
Incidence rate ratio[1] (95% CI)	1.07 [0.88, 1.30]	
Incidence risk ratio[1] (95% CI)	1.09 [0.91, 1.32]	
Seriousness[2,3], N (%)	24 (12.1)	26 (12.0)
Requires hospitalisation	23 (11.6)	26 (12.0)
Prolongs hospitalisation	2 (1.0)	0 (0.0)
Outcome[2,4], N (%)	198 (100.0)	217 (100.0)
Recovered	92 (46.5)	90 (41.5)
Not yet recovered	97 (49.0)	115 (53.0)
Sequelae	1 (0.5)	2 (0.9)
Unknown	8 (4.0)	10 (4.6)
Intensity[2], N (%)	198 (100.0)	217 (100.0)
Mild	99 (50.0)	113 (52.1)
Moderate	79 (39.9)	88 (40.6)
Severe	20 (10.1)	16 (7.4)

[1]Ratio linagliptin vs. placebo

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

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

[4]Each of the outcomes could be individually assigned to an event, i.e. fatal would not be a subset of not recovered

Data source: data on file, 8-05-output-rmp-carmelina-2018-06-25, Table 5.1.5

Clinical trial data (Trial 1218.74 - CAROLINA)

The higher rates of arthralgia in CAROLINA compared to SAF-2 and CARMELINA reflect the longer treatment exposure in CAROLINA; however, the overall frequency of arthralgia-related AEs in CAROLINA and event characteristics such as seriousness, outcome and intensity were balanced between the treatment groups as shown in SVII.Table 10. Events coding to the PT 'arthralgia' were reported at the same frequency (10.5%) in both treatment groups (data source, 1218.74 CTR [c23238241-01], Table 12.1.5.3: 1).

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SVII.Table 10 Overview on arthralgia CAROLINA - (TS_D)

	Glimepiride	Linagliptin
Number of patients treated, N (%)	3000 (100.0)	3014 (100.0)
Total overall time at risk (PY)	12189.7	12337.5
Patients with Arthralgia, risk rate N (%)	727 (24.2)	721 (23.9)
Risk rate [95% CI]	[22.7, 25.8]	[22.4, 25.5]
Incidence rate (/100 PY) [95% CI]	5.96 [5.55, 6.41]	5.84 [5.43, 6.29]
Incidence rate ratio* [95% CI]	0.98 [0.88, 1.09]	
Risk ratio* [95% CI]	0.99 [0.90, 1.08]	
Seriousness#, N (%)	90 (12.4)	87 (12.1)
Disability	0 (0.0)	1 (0.1)
Required hospitalisation	88 (12.1)	85 (11.8)
Prolonged hospitalisation	1 (0.1)	0 (0.0)
Other comparable medical criteria	3 (0.4)	2 (0.3)
Outcome#~, N (%)		
Recovered	300 (41.3)	305 (42.3)
Not yet recovered	396 (54.5)	398 (55.2)
Sequelae	5 (0.7)	5 (0.7)
Fatal	0 (0.0)	0 (0.0)
Unknown	26 (3.6)	13 (1.8)
Intensity#, N (%)		
Mild	371 (51.0)	370 (51.3)
Moderate	312 (42.9)	304 (42.2)
Severe	44 (6.1)	47 (6.5)

* Ratio Linagliptin vs. Glimepiride ("risk ratio" was previously referred to as "incidence risk ratio").
# Percentages are calculated using the number of all patients with Arthralgia as denominator.
%_Patients can be counted in more than 1 seriousness category.
~ Outcome categories are mutually exclusive.
Data source: data on file: xlinarmp—08—study-report-body, Table 5.1.5

Conclusion

Data from the clinical trials including pooled results from randomised, placebo-controlled trials with linagliptin (SAF-2) and findings from CARMELINA do not suggest an increased risk of arthralgia with linagliptin as compared to placebo. Incidence risk and incidence rate ratios were close to 1 in all analyses showing no substantial differences between treatment groups. Findings from CAROLINA were similar, with comparable rates of arthralgia in the linagliptin and glimepiride groups. In view of this conclusion and the fact that no additional pharmacovigilance activities or risk minimisation measures are planned for this safety concern, BI proposes to remove arthralgia as an important potential risk for linagliptin.

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Cardiac failure
The risk of cardiac failure with linagliptin use was evaluated following the saxagliptin CV outcome study SAVOR-TIMI 53. The study results suggested that saxagliptin treatment may be associated with an increased risk of hospitalisation for heart failure.

Evidence from preclinical studies suggests that DPP-4 inhibitors may have cardio-protective effects. In the non-diabetic 5/6 nephrectomy rat model of uraemia, expression of fibrosis markers (TGF β, tissue inhibitor of metalloproteinases, collagen type 1α1 and 3α1) was significantly increased in the heart tissue of placebo-treated uremic rats, compared with sham animals. Short-term treatment with linagliptin for 4 days abolished this effect. Furthermore, levels of mRNA for BNP, a marker of cardiac function, were significantly reduced in heart tissue of linagliptin-treated animals, implying a protective effect on cardiac function. In recent experiments, 2 pathways were identified as possibly being responsible for the cardio-protective effects of DPP-4 inhibitors. These were the reduced degradation of GLP-1 and type 1 SDF-1α [P12-10018].

However, a potential, unfavourable interaction between DPP-4 inhibitors and ACE inhibitors has been proposed. DPP-4 cleaves several vasoactive substrates, and is the main enzyme to cause substance P inactivation during ACE inhibition. Notably, in one study in individuals with metabolic syndrome, sitagliptin attenuated the systemic hypotensive response to an acutely administered ACE inhibitor with concomitant increases in heart rate and noradrenaline concentrations. The investigators postulated that increased concentrations of active substance P, although not measured, could have mediated the observed unfavourable effects [R11-0979].

Additionally, DPP-4 degrades NPY, a neurotransmitter in postganglionic sympathetic nerves. Since NPY is released with noradrenaline and augments its vasoconstrictor responses via Y1-receptor activation, reduced NPY degradation could enhance the negative vascular effect of concurrent DPP-4 and ACE inhibition. Based on these mechanistic data, combining DPP-4 and ACE inhibitors might result in augmented vasopressor response and increased heart rate [R15-0610].

BI provided a detailed assessment of cardiac failure in a White Paper "Assessment of Risk of Heart Failure in DPP-4 inhibitors and Linagliptin", in appendix 12 of the Trajenta RMP, version 9.1, dated 29 Apr 2015 [s00016631-15]. The conclusion of that assessment, based on non-clinical, clinical, post-marketing and epidemiological evidence, was that the data at that time did not support a causal relationship between use of linagliptin and heart failure.

In trials conducted prior to the CV outcome trials, small numbers of cardiac failure events had been reported; these occurred more frequently in patients treated with linagliptin than in those treated with either comparators or placebo. However in the CV outcome trials, cardiac failure events were balanced between the placebo and linagliptin treatment groups in CARMELINA and between the glimepiride and linagliptin treatment groups in CAROLINA.

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Patients with cardiac failure were identified using the narrow SMQ 'cardiac failure'(20000004). In the CARMELINA and CAROLINA trials, cardiac events 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 type 2 diabetes mellitus (SAF-2)

In SAF-2, the rate of cardiac failure based on a small number of AEs was higher in the linagliptin group than in the placebo group (0.4 vs. 0.2, respectively). In nearly 50% of these events the outcome was reported as recovered. Most of these events in linagliptin arm were mild to moderate in intensity (62%).

Trial 1218.22 (CARMELINA)

The following table provides an overview of the Cox regression analyses based on the TS for the adjudicated endpoint 'hospitalisation for heart failure', 'CV death or hospitalisation for heart failure', and 'all-cause mortality or hospitalisation for heart failure'. For all endpoints, the proportions of patients with an event for the analyses based on the TS were balanced between the linagliptin treatment group and the placebo group, with all 95% CIs of the HRs containing 1.

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SVII.Table 11 Cox regression for endpoints related to heart failure requiring hospitalisation (TS)

	Placebo	Linagliptin
Hospitalisation for heart failure		
Analysed patients (TS), N (100.0%)	3485	3494
Patients with event, N (%)	226 (6.5)	209 (6.0)
Incidence rate per 1000 years at risk	30.4	27.7
Hazard ratio vs. placebo (95% CI)[1]	-	0.90 (0.74, 1.08)
p-value	-	0.2635
CV death or hospitalisation for heart failure		
Analysed patients (TS), N (100.0%)	3485	3494
Patients with event, N (%)	422 (12.1)	406 (11.6)
Incidence rate per 1000 years at risk	56.6	53.7
Hazard ratio vs. placebo (95% CI)[2]	-	0.94 (0.82, 1.08)
p-value	-	0.3881
All-cause mortality or hospitalisation for heart failure		
Analysed patients (TS), N (100.0%)	3485	3494
Patients with event, N (%)	518 (14.9)	499 (14.3)
Incidence rate per 1000 years at risk	69.4	65.9
Hazard ratio vs. placebo (95% CI)[3]	-	0.95 (0.84, 1.07)
p-value	-	0.4012

[1]Based on a Cox regression model with terms for treatment group (p=0.2635), region (p=0.0012), history of heart failure (p=<0.0001).

[2]Based on a Cox regression model with terms for treatment group (p=0.3881), region (p=<0.0001), history of heart failure (p=<0.0001).

[3]Based on a Cox regression model with terms for treatment group (p=0.4012), region (p=<0.0001)

Data source: 1218.22 CTR [c22196815-02], Tables 15.2.16.1.1, 15.2.17.1.1, 15.2.31.1

The results for time to first hospitalisation for heart failure (based on adjudicated events) were generally consistent across subgroups for each endpoint (SVII.Figure 1). No treatment interaction was observed for the subgroups, e.g. “history of heart failure” and “prevalent kidney disease at baseline”. For patients with or without insulin at baseline a significant subgroup by treatment interaction favouring linagliptin in patients without insulin vs. a neutral result in those on insulin was observed.

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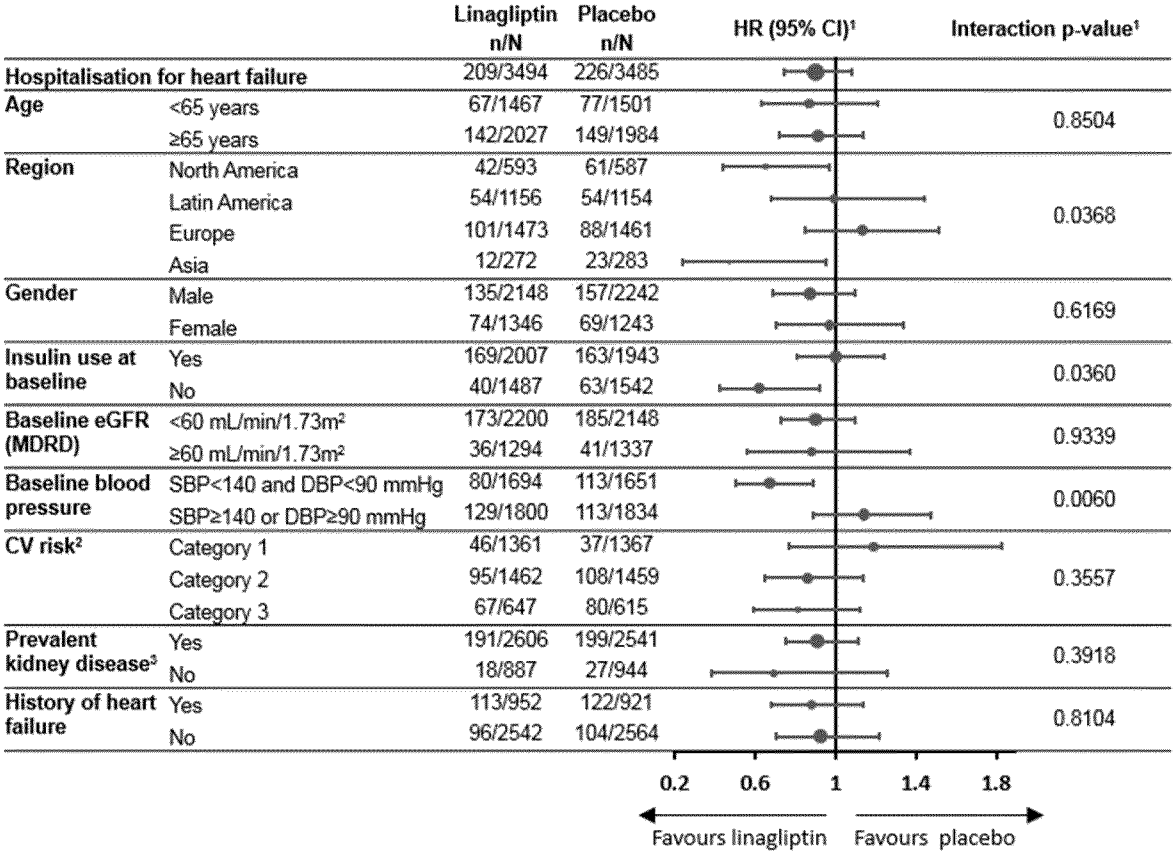
SVII.Figure 1 Subgroup analyses for time to first hospitalisation for heart failure



[1]Cox regression model with terms for treatment group, region, subgroup, and treatment-by-subgroup interaction.

[2]Categories: (1) Established macrovascular disease and albuminuria without established renal disease, (2) Established renal disease without macrovascular and albuminuria disease, (3) Established macrovascular disease and albuminuria and established renal disease.

[3]Defined as: eGFR <60 mL/min/1.73 m² or macroalbuminuria UACR >300 mg/g.

The bubble size for the HR point estimate is proportional to the number of patients in the subgroup.

Data source: 1218.22 CTR [c22196815-02], Figure 11.1.3.5.1: 2.

Heart failure AEs

Heart failure was also analysed based on investigator-reported AEs as defined by the narrow SMQ 'cardiac failure'. For heart failure AEs, considering the time until study end, results were consistent with those seen for adjudicated heart failure events. Although a slightly higher rate of events was reported in the placebo treatment group than in the linagliptin group, the difference is not considered to be significant since the 95% CI of the HR includes 1 (SVII.Table 12).

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SVII.Table 12 Cox regression of heart failure adverse events considering the time until study end (based on SMQ) - TS

	Placebo	Linagliptin
Analysed patients (TS), N (100.0%)	3485	3494
Patients with event, N (%)	305 (8.8)	276 (7.9)
Incidence rate per 1000 years at risk	41.4	36.9
Hazard ratio vs. placebo (95% CI)[1]	-	0.89 (0.76, 1.05)
p-value	-	0.1697

[1]Based on a Cox regression model with terms for treatment group (p=0.1697), region (p=0.9072), history of heart failure (p=<0.0001).

Data source: 1218.22 CTR [c22196815-02], Table 15.2.30.1.2

Trial 1218.74 (CAROLINA)

Hospitalisation for heart failure, hospitalisation for or death from heart failure, and hospitalisation for heart failure or CV death were tertiary CV endpoints. No significant treatment differences were observed for these endpoints. Similar results were seen in an additional analysis of heart failure or all-cause mortality (SVII.Table 13).

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SVII.Table 13 Occurrence and time to occurrence of different heart failure analyses (TS)

	Glimepiride	Linagliptin
Number of patients, N (%)	3010	3023
Hospitalisation for heart failure		
Number of patients with event, N (%)	92 (3.1)	112 (3.7)
95% CI[1] [%]	(2.5, 3.7)	(3.1, 4.4)
Incidence rate per 1000 years at risk	5.3	6.4
Comparison vs. glimepiride		
HR (95% CI)[2]		1.21 (0.92, 1.59)
p-value for HR=1.0[3] (two-sided)		0.1761
Hospitalisation for or death from heart failure		
Number of patients with event, N (%)	97 (3.2)	115 (3.8)
95% CI[1] [%]	(2.6, 3.9)	(3.2, 4.5)
Incidence rate per 1000 years at risk	5.6	6.6
Comparison vs. glimepiride		
HR (95% CI)[2]		1.18 (0.90, 1.54)
p-value for HR=1.0[3] (two-sided)		0.2355
Hospitalisation for heart failure or CV death		
Number of patients with event, N (%)	234 (7.8)	236 (7.8)
95% CI[1] [%]	(6.9, 8.8)	(6.9, 8.8)
Incidence rate per 1000 years at risk	13.4	13.4
Comparison vs. glimepiride		
HR (95% CI)[2]		1.00 (0.84, 1.20)
p-value for HR=1.0[3] (two-sided)		0.9671
All-cause mortality or hospitalisation for heart failure		
Number of patients with event, N (%)	392 (13.0)	372 (12.3)
95% CI[1] [%]	(11.9, 14.3)	(11.2, 13.5)
Incidence rate per 1000 years at risk	22.3	21.1
Comparison vs. glimepiride		
HR (95% CI)[2]		0.94 (0.82, 1.09)
p-value for HR=1.0[3] (two-sided)		0.4276

[1] Wilson CI.

[2] Hazard ratio and CI derived from Cox's proportional hazards model with factor treatment.

[3] p-value derived from Wald's chi-square test

Data source: 1218.74 CTR [c23238241-01], Tables 11.1.2.3.5:1 and 11.1.2.3.6: 1

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Subgroup analyses for hospitalisation for heart failure were prepared post hoc. There were no clinically meaningful differences across subgroup categories

Heart failure AEs
In addition to the analyses of the adjudicated heart failure endpoints, the occurrence of and time to first investigator-reported heart failure, based on the narrow SMQ 'cardiac failure', was a tertiary CV endpoint. No significant treatment differences were observed for this endpoint (SVII.Table 14) (data source: 1218.74 CTR [c23238241-01], Table 11.1.2.3.5: 2).

SVII.Table 14 Occurrence and time to occurrence of investigator-reported heart failure – TS_D

	Glimepiride	Linagliptin
Number of patients, N (%)	3000	3014
Number of patients with event, N (%)	155 (5.2)	166 (5.5)
95% CI[1] [%]	(4.4, 6.0)	(4.7, 6.4)
Incidence rate per 1000 years at risk	9.0	9.5
Comparison vs. glimepiride		
HR (95% CI)[2]		1.06 (0.85, 1.32)
p-value for HR=1.0[3] (two-sided)		0.5844

[1] Wilson CI.
[2] Hazard ratio and CI derived from Cox's proportional hazards model with factor treatment.
[3] p-value derived from Wald's chi-square test
Data source: [c23238241-01], Table 11.1.2.3.5:2

Conclusion
The robust data from CARMELINA, a placebo-controlled study performed in a highly vulnerable T2DM population with established macrovascular or renal disease, showed no risk of the pre-specified end point of HHF or other composite end points with HHF. For all endpoints, the proportions of patients with an event were balanced between the linagliptin treatment group and the placebo group. Analyses based on the narrow SMQ 'cardiac failure' were also consistent with results from adjudicated events. Although conducted in a different population at lower CV risk with only 4.5% of subjects reporting heart failure at baseline compared with 26.8% in CARMELINA, the CAROLINA study results were similar, showing no significant treatment differences for the investigator-reported heart failure events or the adjudicated endpoints HHF, HHF or death from heart failure, HHF or CV death, or HHF or all-cause mortality.

Considering that evidence has shown a neutral effect of linagliptin on adjudicated heart failure outcomes in the CV outcome trials as well as investigator-reported heart failure and no causal association between use of linagliptin and an increased risk of cardiac failure, BI proposes to remove cardiac failure as an important potential risk from the RMP based on the GVP module V revision 2 guidance.

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Missing information

Removal of the following topics from the list of missing information:

- Elderly patients >80 years
- Malignancies
- Patients with a history of cardiovascular events

Elderly patients >80 years

Few patients older than 80 years were included in the clinical trials of linagliptin prior to the CV outcome trials 1218.22 (CARMELINA) and 1218.74 (CAROLINA). In trial 1218.63 which did include patients ≥70 years of age, and trial 1218.149 in which all patients were 60 years of age or older, treatment with linagliptin was efficacious and well tolerated with no safety concerns being raised [U11-1781-02, c11641379-01].

The CV outcome trials enrolled a substantial number of patients ≥80 years of age and thus serve as the source for safety data in this population. Results relevant for this topic are summarised below.

Trial 1218.22 (CARMELINA)

412 patients (5.9%) ≥80 years of age were treated in this trial, 220 with linagliptin, and 192 with placebo. For the subgroup of patients ≥80 years the overall frequency of AEs was higher in the placebo group (85.4%) than in the linagliptin group (80.5%). The proportions of subjects with severe AEs, SAEs, AEs leading to treatment discontinuation and AEs leading to death were similar between the 2 treatment groups (Data source, data on file, 1218.22 CTR [c22196815-02], Tables 15.3.1.1.2, 15.3.1.3.7 and 15.3.1.3.23).

For the subgroup of patients ≥80 years of age, investigator-defined AEs indicative of hypoglycaemia were reported more often in the placebo group than in the linagliptin group (30.7% vs. 28.6%, respectively). This was also the case for the subset of patients with symptomatic hypoglycaemic AEs or any severe hypoglycaemic AE 26.6% of placebo-treated patients compared with 20.9% of patients treated with linagliptin (Data source, data on file, 1218.22 CTR [c22196815-02], Table 15.3.1.6.5).

The outcome of a subgroup analysis on the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (3P-MACE) did not demonstrate that age was an effect modifier for the occurrence of primary endpoint events (p-value of the age-by-treatment interaction = 0.1817).

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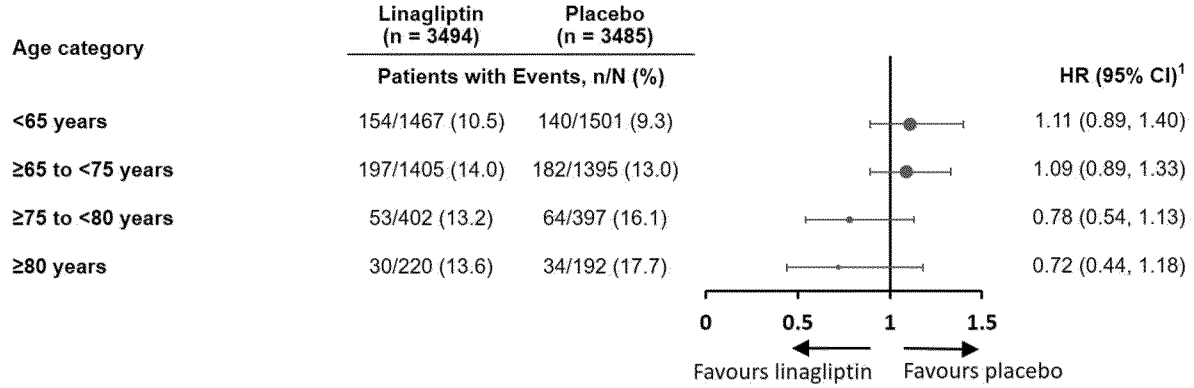
SVII.Figure 2 Subgroup analysis for the time to 3P-MACE by age in the CARMELINA trial



[1] Cox's proportional hazards model. Hazard ratio adjusted for factors treatment, subgroup, and subgroup-by-treatment interaction

Data source: data on file, 8-05-1218-0022-030103-190722, Table 1.3.2.1

Subgroup analyses of other AEs of special interest in general showed similar frequencies between linagliptin- and placebo-treated patients. In some cases, the small differences noted between treatment groups were considered not meaningful due to small number of events and were not supported by other age subgroups.

Trial 1218.74 (CAROLINA)
In the CAROLINA trial, 846 (14.0%) of patients were ≥75 years old (linagliptin: 410, glimepiride: 436) and 197 patients (3.3%) were ≥80 years (linagliptin: 94, glimepiride: 103). In the AE overall summary by subgroup, there was a trend towards a lower frequency of patients with AEs of severe intensity in elderly patients (≥75 years) in the linagliptin group (38.5%) compared with the glimepiride group (47.9%). The difference was consistent in patients aged ≥80 years (data source: data on file 1218.74 CTR [c23238241-01], tables 15.1.4.1: 1, 15.3.1.2.1: 1 and 15.3.1.2.1: 11).

The frequency of SAEs, AEs with a fatal outcome, and AEs leading to treatment discontinuation increased with higher age subgroups. In the small subgroup of patients aged ≥80 years, the frequency of patients with SAEs was lower in the linagliptin group (64.9%) than in the glimepiride group (73.8%). AEs with a fatal outcome occurred at a similar frequency in both treatment groups, but the number of cases in this subgroup of patients was too small to conclude a trend. AEs leading to treatment discontinuation also occurred at similar frequencies in both treatment groups (data source, 1218.74 CTR [c23238241-01], Appendix 16.1.13.1, tables 8.2.1.1, 8.2.2.1 and 8.2.3.1).

As with the overall population, investigator-defined AEs indicative of hypoglycaemia for the subgroup of patients ≥80 years of age, were reported less frequently in the linagliptin group than in the glimepiride group (12.8% vs. 35.0%, respectively). Hence the treatment effect was overall consistent across age categories. This was also the case for the subset of patients with PG <54 mg/dL or severe hypoglycaemic AE (3.2% vs. 19.4% for linagliptin and glimepiride,

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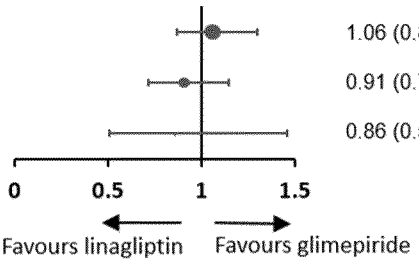
respectively) and those with a severe hypoglycaemic AE (0% vs. 8.7% for linagliptin and glimepiride, respectively) (data source, 1218.74 CTR [c23238241-01], Table 12.1.3: 2).

An additional subgroup analysis was conducted on elderly patients aged ≥80 years. Similar to CARMELINA, the p-value of the age-by-treatment interaction was 0.5393, not demonstrating that age was an effect modifier for the occurrence of primary endpoint events.

SVII.Figure 3 Subgroup analysis for the time to 3P-MACE by age in the CAROLINA trial

Age category	Linagliptin (n = 3023)	Glimepiride (n = 3010)	HR (95% CI)[1]
	Patients with Events, n/N (%)		
<70 years	196/2018 (9.7)	182/1984 (9.2)	1.06 (0.87, 1.30)
≥70 to <80 years	135/911 (14.8)	149/923 (16.1)	0.91 (0.72, 1.15)
≥80 years	25/94 (26.6)	31/103 (30.1)	0.86 (0.51, 1.46)



[1] Cox's proportional hazards model. Hazard ratio adjusted for factors treatment, region, subgroup, and subgroup-by-treatment interaction

Data source: data on file, 8-05-1218-0074-01-072-190717, Table 72.1.1

Subgroup analyses of other AEs of special interest showed that the frequency of renal AEs increased with increasing age category, but there were no clinically meaningful differences between treatment groups for renal AEs or any other AEs of special interest in patients ≥80 years of age.

Although not formally designated as an AE of special interest, arthralgia was reported less frequently in the linagliptin group than in the glimepiride group (26.6% vs. 33.0%, respectively) in patients ≥80 years of age. Furthermore, within the linagliptin group, there was little difference in the incidence of arthralgia across age groups, ranging from 23.1% in patients <65 years of age to 26.6% in those ≥80 years of age (data source: data on file, xlinarmp—08—study-report-body, Table 2.1.5.8).

Conclusions
As might be expected, the overall frequency of AEs, SAEs, fatal AEs and AEs leading to treatment discontinuation tended to increase with increasing age category, but differences between treatment groups were minimal in both trials. Similar patterns were seen for AEs of special interest when analysed in this subgroup of patients. In summary, the findings from the CV outcome trials with a combined total of over 600 treated patients ≥80 years of age did not show any substantial differences in the safety profile in this subgroup of patients compared with the overall trial populations. In view of these findings, BI proposes to remove elderly patients >80 years as a missing information topic.

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Malignancies
Non-clinical studies provided no evidence of a potential link between cancer risk and linagliptin treatment.

Clinical trial data
For the pooled clinical trial data, patients with malignancies were identified using the SMQ 'Malignancies' (narrow). In the CARMELINA and CAROLINA trials, patients with malignancies were identified using the SMQs "Malignant Tumours" and "Tumours of unspecified malignancy".

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

SVII.Table 15 provides an overview of all malignancy events for SAF-2. The proportion of patients reporting malignancies was the same in each treatment group. SAEs were reported by a higher proportion of placebo treated subjects than those in the linagliptin group. A majority of subjects in each treatment group reported AEs of severe intensity, with a larger proportion in the placebo group. 5 events of malignancy, all in placebo-treated patients, had a fatal outcome.

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SVII.Table 15 Overview on malignancy (SAF-2)

	Placebo	Linagliptin
Number of patients treated, N (%)	4936 (100.0)	7136 (100.0)
Total overall time at risk (PY)	3202.48	4161.14
Patients with malignancies, N (%)	31 (0.6)	42 (0.6)
95% CI	[0.4, 0.9]	[0.4, 0.8]
Rate/100 PY	0.97	1.01
Incidence rate ratio[1] (95% CI)	1.20 [0.8, 1.9]	
Incidence risk ratio[1] (95% CI)	1.22 [0.8, 1.9]	
Seriousness[2,3], N (%)	27 (87.1)	30 (71.4)
Resulted in death	5 (16.1)	0 (0.0)
Immediately life-threatening	1 (3.2)	1 (2.4)
Disability	0 (0.0)	1 (2.4)
Required hospitalisation	14 (45.2)	15 (35.7)
Prolonged hospitalisation	1 (3.2)	1 (2.4)
Other	18 (58.1)	16 (38.1)
Outcome[2,4], N (%)		
Recovered	12 (38.7)	17 (40.5)
Not yet recovered	12 (38.7)	22 (52.4)
Sequelae	1 (3.2)	1 (2.4)
Fatal	5 (16.1)	0 (0.0)
Unknown	1 (3.2)	2 (4.8)
Intensity[2], N (%)		
Mild	4 (12.9)	10 (23.8)
Moderate	11 (35.5)	14 (33.3)
Severe	16 (51.6)	18 (42.9)

[1]Ratio linagliptin vs. placebo

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

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

[4]Each of the outcomes could be individually assigned to an event, i.e. fatal would not be a subset of not recovered.

Data source: data on file, 8-05-output-rmp-2017-final, Table 7.2.14

Trial 1218.22 (CARMELINA)

Overall, a balanced proportion of patients had at least one cancer during the entire study period, as reported by the investigator (3.3% vs. 3.8%, in the linagliptin and placebo groups, respectively), with incidence rates per 100 PY of 1.51 and 1.76 for the linagliptin and placebo groups, respectively (Data source: 1218.22 CTR [c22196815-02], Table 12.1.5:1 and 15.3.1.8.1).

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SVII.Table 16 Frequency of patients with events of cancer overall and related to trial drug by the investigator (TS – 1218.22)

	Placebo	Linagliptin
Patients with at least 1 cancer	134 (3.8)	116 (3.3)
Patients with at least 1 event in the SMQ "malignant tumours"	123 (3.5)	106 (3.0)
Patients with at least one event in the SMQ "tumours of unspecified malignancy"	14 (0.4)	13 (0.4)
Patients with at least 1 cancer related to treatment	3 (0.1)	3 (0.1)
Patients with at least 1 event in the SMQ "malignant tumours"	2 (0.1)	2 (0.1)
Patients with at least one event in the SMQ "tumours of unspecified malignancy"	1 (0.1)	1 (0.1)

All AEs occurring between first study drug intake and study end are taken into account

Tumours were flagged using SMQ 20000194 "Malignant Tumours" and SMQ 20000195 "Tumours of unspecified malignancy", respectively.

Data source: 1218.22 CTR [c22196815-02], Table 12.1.5: 1

A separate independent, blinded, external committee reviewed all events suspected of solid cancer and assessed whether the cancer case was possibly related, not related or not assessable. The frequencies of cancer events assessed as possibly related to trial medication were low and balanced in both treatment groups (0.4% vs. 0.7% linagliptin vs. placebo) (Data source: 1218.22 CTR [c22196815-02], Table 12.1.5: 2).

Trial 1218.74 (CAROLINA)

The proportions of patients who had at least 1 event of 'malignancy' reported by the investigator during the entire study period were similar in the linagliptin group and in the glimepiride group (9.3% vs. 10.1%, in the linagliptin and glimepiride groups, respectively) with incidence rates per 100/PY of 1.59 and 1.74 for the linagliptin and glimepiride groups, respectively (SVII.Table 17 and 1218.74 CTR, Table 8.3.8.1).

SVII.Table 17 Patients reported with AE terms associated with malignancy - TS

	Glimepiride	Linagliptin
	N (%)	N (%)
Number of patients	3010 (100.0)	3023 (100.0)
Patients with at least 1 malignancy event	303 (10.1)	280 (9.3)
Narrow SMQ "malignant tumours"	287 (9.5)	273 (9.0)
SMQ "tumours of unspecified malignancy"	18 (0.6)	11 (0.4)

Data source: 1218.74 CTR [c23238241-01], Table 12.1.5.1:1

For patients with a minimum exposure of 6 months, the proportions of patients with at least 1 event of 'malignancy' were 8.4% in the linagliptin group and 9.7% in the glimepiride Group (data source: 1218.74 CTR [c23238241-01], Appendix 16.1.13.1, Table 8.3.8.2). A separate independent, blinded, external committee reviewed all events suspected of solid

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cancer and assessed whether the cancer case was possibly related, not related or not assessable. Most events were assessed as not related in both treatment groups. The frequencies of patients with malignancy events that were adjudicated by the Oncology Assessment Committee as possibly related to study medication were low and balanced in both treatment groups (2.8% vs. 3.7% linagliptin vs. glimepiride) (data source: 1218.74 CTR [c23238241-01], Table 12.1.5.1:2).

Conclusion
In the SAF-2 pool of randomised, placebo-controlled trials of linagliptin, malignancies occurred at the same rate (0.6%) in the linagliptin and placebo groups. In the CV outcome trials, malignancies were also reported at comparable frequencies up to trial end between treatment groups in CARMELINA (3.3% vs. 3.8% for linagliptin and placebo, respectively) and in CAROLINA (9.3% vs. 10.1% for linagliptin and glimepiride, respectively) with corresponding incidence rates that were similar between treatment groups and between the trials. Malignancies considered to be possibly treatment related, as assessed by an independent Oncology Assessment Committee, were also reported at similar frequencies in the CV outcome trials.

With over 13 000 patients treated, including over 800 patients reporting some type of malignancy, CARMELINA and CAROLINA allowed for a more in-depth assessment of malignancies than was possible based on the pool of randomised, placebo-controlled trials of linagliptin (SAF-2). Considering the substantial additional data provided from CARMELINA and CAROLINA, and the fact that results from these trials did not show any increased risk of malignancy with linagliptin compared with placebo or an active comparator, BI proposes to remove malignancy as missing information. Pancreatic cancer will continue to be monitored as an important potential risk.

Patients with a history of cardiovascular events
Data from clinical studies did not reveal an increase in the risk of CV events upon use of linagliptin. On the contrary, CV events rather occurred at a lower frequency with linagliptin as compared to other medicines used as comparators. The number of events in the clinical studies was low, however, precluding firm conclusions.

In a prospective, meta-analysis of independently adjudicated CV events from 19 phase III clinical studies involving 9459 patients with T2DM, linagliptin treatment was not associated with an increase in CV risk. This included patients with a known history of coronary artery disease and cerebrovascular disease. 691 (11.8%) of patients on linagliptin treatment, and 491 (13.6%) on comparators had a history of coronary artery disease, and 212 (3.6%) of patients on linagliptin treatment, and 170 (4.7%) on comparators had a history of cerebrovascular disease. The primary endpoint, the composite of the occurrence or time to first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for unstable angina, was non-significantly lower for linagliptin versus combined active and placebo comparators (HR 0.78; 95% CI 0.55, 1.12). In total, there were 60 primary events on linagliptin and 62 on comparators.

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CV events were observed to occur at a similar rate between linagliptin and placebo (HR 1.09; 95% CI 0.68, 1.75). In placebo controlled studies, in total there were 43 (1.03%) primary events on linagliptin and 29 (1.35%) on placebo. Linagliptin treatment was not associated with an increase in CV risk compared with combined comparators [U12-2369-01].

Results from the CARMELINA trial (1218.22), which was designed to investigate the long-term impact of linagliptin on CV morbidity and mortality in a cardiovascular high-risk population of patients with T2DM and established macrovascular or renal disease, were consistent with findings of the meta-analysis described above providing further evidence that treatment with linagliptin does not increase the risk of CV events.

The primary endpoint in the trial was time to the first occurrence of any of the following adjudication-confirmed components of the primary composite endpoint (3-point MACE): CV death, non-fatal MI or non-fatal stroke. As per the inclusion criteria, the treated patients all had a high risk of CV events.

A total of 854 patients were reported with an adjudication-confirmed primary endpoint event including 434 patients (12.4%) with an event in the linagliptin group and 420 patients (12.1%) in the placebo group. The HR based on Cox proportional hazards regression model for linagliptin vs. placebo was 1.02 (95% CI 0.89, 1.17). Linagliptin was therefore demonstrated to be non-inferior to placebo with an upper bound of the 95% CI of below 1.3 and not superior to placebo.

Consistent results for the treatment effect were also generally observed across the subgroups displayed in SVII.Figure 4. Because of the macrovascular component, the CV risk categories 1 (Established macrovascular disease and albuminuria without established renal disease) and 3 (Established macrovascular disease and albuminuria and established renal disease) are the most relevant to this missing information topic. No significant difference in the treatment effect was observed for the CV categories or other subgroups, including age, insulin use at baseline, prevalent kidney disease at baseline or baseline eGFR.

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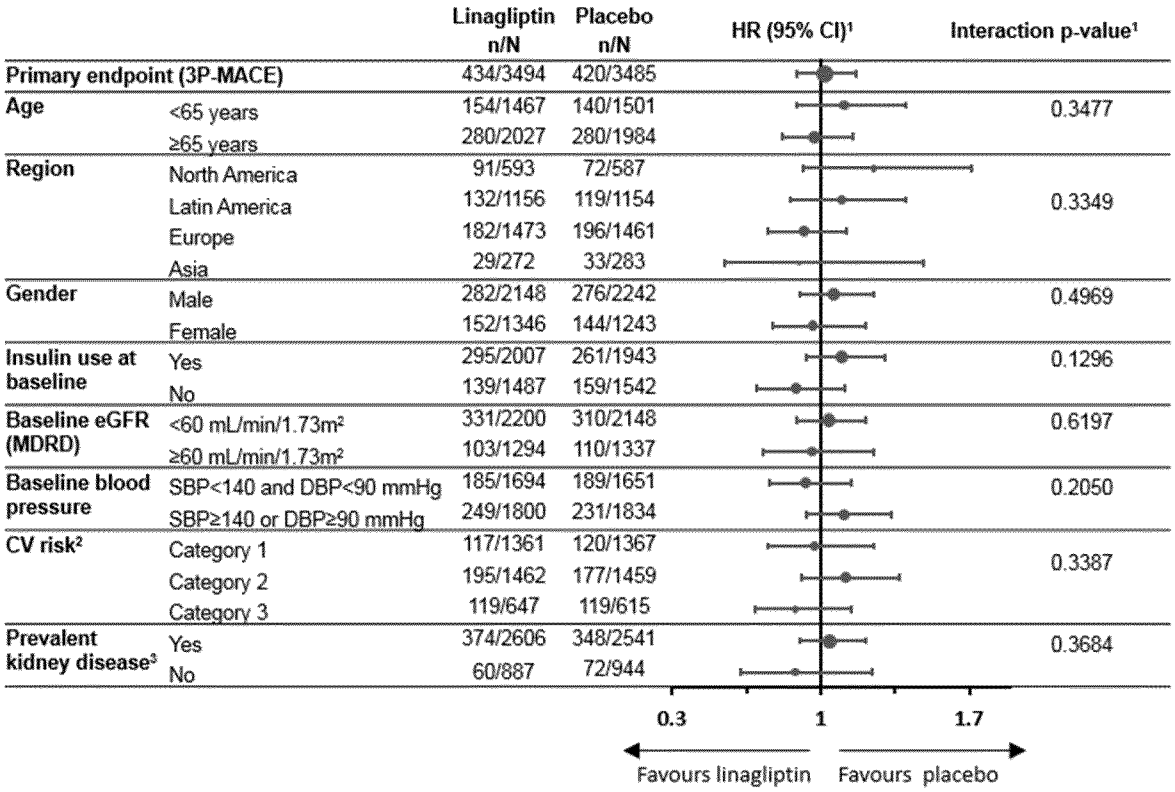
SVII.Figure 4 Subgroup analysis for time to 3P-MACE



[1]Cox regression model with terms for treatment group, region, subgroup, and treatment-by-subgroup interaction.

[2]Categories: (1) Established macrovascular disease and albuminuria without established renal disease (2) Established renal disease without macrovascular and albuminuria disease (3) Established macrovascular disease and albuminuria and established renal disease.

[3]Defined as: eGFR <60 mL/min/1.73 m² or macroalbuminuria UACR >300 mg/g.

N, total number of patients in the subgroup; n, number of patients with event; the bubble size for the HR point estimate is proportional to the number of patients in the subgroup.

Data source: [c22196815-02], Figure 11.1.1.3: 1

CARMELINA 3P-MACE summary:

Subgroup analyses for the occurrence of both the primary endpoint 3P-MACE and the cardiovascular death component showed some fluctuation across HbA_{1c} categories but no evidence of an elevated risk of MACE associated with increasing HbA_{1c} in patients treated with linagliptin. The difference in HR for 3P-MACE by the HbA_{1c} categories <8% and ≥8% (0.9 and 1.2, respectively) is therefore rather considered a chance finding.

Overall, there was no clinically meaningful imbalance between the treatment groups in the proportion of patients with any AE, SAE or AE leading to discontinuation. No clinically meaningful differences were observed for the subgroup analyses and the overall safety profile for linagliptin was comparable to the placebo group across the various subgroups. There was also no increased risk for hospitalisation for heart failure or any other heart failure endpoint. In summary, cardiovascular and renal safety of linagliptin have been demonstrated in this CV high risk population with established macrovascular or prevalent kidney disease.

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Results from the CAROLINA trial (1218.74), which was designed to investigate the long-term impact of linagliptin on CV morbidity and mortality in patients with T2DM at elevated cardiovascular risk provided further evidence that treatment with linagliptin does not increase the risk of CV events. The primary endpoint in this trial was time to first 3P-MACE, i.e. the time to first occurrence of any of the following adjudication-confirmed components of the primary composite endpoint: CV death, non-fatal MI or non-fatal stroke.

There were 356 patients (11.8%) with a 3P-MACE event in the linagliptin group and 362 patients (12.0%) in the glimepiride group in the TS. The incidence rate per 1000 years at risk was 20.7 for linagliptin and 21.2 for glimepiride. The HR based on Cox's proportional hazards model for linagliptin vs. glimepiride was 0.98 (95.47% CI 0.84, 1.14). Linagliptin was therefore demonstrated to be:

1. Non-inferior to glimepiride as the upper bound of the 95.47% CI was below 1.3.
2. Not superior to glimepiride as the upper bound of the 95.47% CI was above 1.0.

The Kaplan-Meier estimates of time to first occurrence of 3P-MACE for linagliptin vs. glimepiride over time are presented in SVII.Table 18 and SVII.Figure 5.

SVII.Table 18 Time to first 3P-MACE - TS

	Glimepiride	Linagliptin
Number of patients, N (%)	3010	3023
Number of patients with event, N (%)	362 (12.0)	356 (11.8)
95% CI[1] [%]	10.9, 13.2	10.7, 13.0
Time at risk for event [years]	17 103.7	17 205.5
Incidence rate per 1000 years at risk	21.2	20.7
Time to event [months]		
2.5% quantile	15.3	16.8
5.0% quantile	33.1	31.7
7.5% quantile	47.0	46.8
10.0% quantile	59.3	62.4
Comparison vs. glimepiride		
Hazard ratio (95.47% CI)[2]		0.98 (0.84, 1.14)
p-value for HR ≥1.3 (one-sided)[3]		<0.0001
p-value for HR ≥1.0 (one-sided)[3]		0.3813
p-value for HR =1.0 (one-sided)[3]		0.7625

[1] Wilson CI

[2] Hazard ratio and CI derived from Cox's proportional hazards model with factor treatment

[3] p-value derived from Wald's Chi-square test. HR ≥1.3 corresponds to non-inferiority and HR ≥1.0 to superiority analysis.

Data source: 1218.74 CTR [c23238241-01], Table 11.1.1: 1

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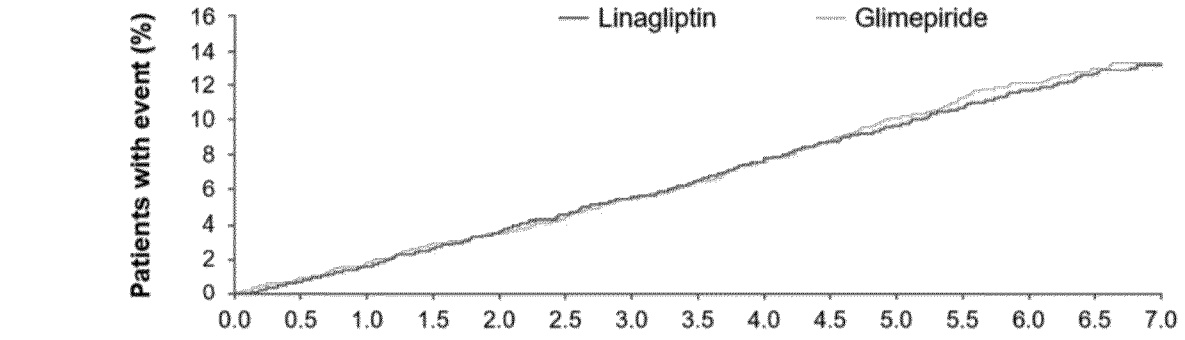
SVII.Figure 5 Kaplan-Meier estimation of time to first occurrence of 3P-MACE over time - TS



No. of patients															
Linagliptin (N)	3023	2957	2901	2846	2803	2762	2725	2679	2627	2582	2534	2451	1830	1040	213
Glimepiride (N)	3010	2940	2890	2833	2797	2757	2710	2662	2618	2569	2509	2414	1865	1020	207

Data source: 1218.74 CTR [c23238241-01], Figure 11.1.1: 1

The proportion of patients with each event type was generally balanced between the treatment groups; see SVII.Table 19.

SVII.Table 19 Distribution of components contributing to the 3P-MACE - TS

	Glimepiride	Linagliptin
Number of patients, N (%)	3010	3023
Number of patients with event, N (%)	362 (12.0)	356 (11.8)
CV death, N (%)	125 (4.2)	129 (4.3)
Non-fatal MI, N (%)	138 (4.6)	141 (4.7)
Non-fatal stroke, N (%)	101 (3.4)	86 (2.8)

The first event per patient contributing to the 3P-MACE endpoint is presented

Data source: 1218.74 CTR [c23238241-01], Table 11.1.1: 2

Consistent results for the treatment effect were generally observed across the subgroups and are in line with the primary endpoint (SVII.Figure 6). Subgroup variables considered to be of particular interest for patients with T2DM were the following risk categories:

- Risk A: previous vascular disease
- Risk B: evidence of vascular related end-organ damage
- Risk C: age ≥70 years
- Risk D: at least two of other prespecified CV risk factors

A summary of the subgroup analysis for Risk A, which is considered to be the most relevant for this missing information topic, is shown in the table below.

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SVII.Table 20 Subgroup analysis for time to first occurrence of any of the CEC confirmed adjudicated components of 3P-MACE (Risk A): Cox regression model - TS

	Glimepiride	Linagliptin
Risk A: History of vascular disease		
No		
Number of patients, N (%)	1962	1963
Number of patients with event, N (%)	162 (8.3)	166 (8.5)
Time at risk for event [years]	11 487.5	11 484.4
Incidence rate per 1000 years at risk	14.1	14.5
Comparison vs. glimepiride		
HR (95% CI)[1]	1.03 (0.83, 1.27)	
p-value	0.8192	
Yes		
Number of patients, N (%)	1038	1051
Number of patients with event, N (%)	199 (19.2)	190 (18.1)
Time at risk for event [years]	5613.9	5721.1
Incidence rate per 1000 years at risk	35.4	33.2
Comparison vs. glimepiride		
HR (95% CI)[1]	0.94 (0.77, 1.14)	
p-value[2]	0.5135	
Interaction p-value	0.5416	

[1] Hazard ratio adjusted for factor treatment, subgroup and subgroup−by−treatment interaction
[2] p−value for subgroup−by−treatment interaction.
Data source: 1218.74 CTR [c23238241-01], Table 15.2.1.6.1: 1

Additional subgroups analysed included gender, region, prior anti-diabetic treatment with an SU or glinide, baseline HbA1c, baseline eGFR, and the time since the diagnosis of diabetes.

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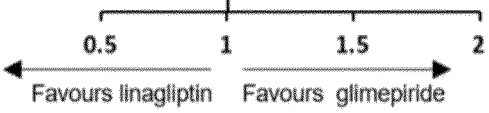
SVII.Figure 6 Subgroup analysis for time to 3P-MACE

		Linagliptin n/N	Glimepiride n/N	HR (95% CI)[1]	Interaction p-value[1]
Primary endpoint (3P-MACE)		356/3023	362/3010		
Risk A	No	166/1963	162/1962		0.5416
	Yes	190/1051	199/1038		
Risk B	No	280/2614	280/2582		0.9467
	Yes	76/400	81/418		
Risk C	<70 years	196/2009	180/1975		0.2110
	≥70 years	160/1005	181/1025		
Risk D	No	93/598	91/606		0.5754
	Yes	263/2416	270/2394		
Gender	Male	250/1838	263/1781		0.2571
	Female	106/1185	99/1229		
Region	Africa	10/64	4/67		0.1686
	Asia	44/465	52/468		
	Europe	176/1422	182/1399		
	North America, New Zealand, Australia	66/618	76/622		
	South America, Mexico	60/454	48/454		
Prior use of SU or glinide	No	234/2117	225/2116		0.2912
	Yes	122/897	136/884		
Baseline HbA_{1c}	<7.0%	133/1255	135/1228		0.8099
	≥7.0%	223/1758	226/1772		
Baseline eGFR (MDRD)	<60 mL/min/1.73m²	248/2419	260/2462		0.9036
	≥60 mL/min/1.73m²	107/592	101/538		
Time since diagnosis of diabetes	≤5 years	131/1224	133/1212		0.5309
	>5 to 10 years	97/848	112/861		
	>10 years	128/942	116/927		



[1] Cox's proportional hazards model. Hazard ratio adjusted for factor treatment, subgroup, and subgroup-by-treatment interaction. p-value for subgroup-by-treatment interaction

Data source: 1218.74 CTR [c23238241-01], Figure 11.1.1: 3

CAROLINA 3P-MACE summary:

The primary endpoint of this trial was the time to first 3P-MACE, i.e. the time to the first occurrence of any of the following adjudication-confirmed components: CV death, non-fatal MI, or non-fatal stroke. The primary endpoint was met and linagliptin was demonstrated to be non-inferior to glimepiride, as the upper bound of the 95.47% CI was below 1.3 ($p<0.0001$). In total, 356 patients (11.8%) were reported with a 3P-MACE event in the linagliptin group and 362 patients (12.0%) in the glimepiride group (HR = 0.98; 95.47% CI 0.84, 1.14). As the upper bound of the 95.47% CI was above 1.0, the next step in the testing hierarchy, the analysis of the primary endpoint for superiority of linagliptin, was not demonstrated (one-sided $p = 0.3813$). The sensitivity analyses on the primary endpoint used different analysis sets and censoring approaches and were consistent with the primary analysis. Likewise,

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consistent results were generally observed across the subgroups and are in line with the primary analysis.

Conclusions
Results from the CV outcome trials, particularly CARMELINA reinforced findings of a meta-analysis of 19 phase III clinical studies involving 9459 patients with T2DM, which found no increased CV risk associated with linagliptin treatment. In the CARMELINA trial, linagliptin was demonstrated to be non-inferior to placebo for time to first occurrence of any of the adjudication-confirmed components of the primary composite endpoint: CV death, non-fatal MI, non-fatal stroke (3P-MACE), with an HR of 1.02 (95% CI 0.89, 1.17) based on Cox proportional hazards regression model for linagliptin vs. placebo. There was also no increased risk for HHF or any other heart failure endpoint. Although not as rigorous due to lack of placebo control and a lower-risk population, CV safety findings from CAROLINA were in line with those seen in CARMELINA where linagliptin was found to be non-inferior to glimepiride with respect to the primary composite endpoint 3P-MACE. Subgroup analyses were consistent with the primary analysis.

With over 13 000 patients treated, including 1572 patients with an adjudication-confirmed CV event, the CARMELINA and CAROLINA trials have established the cardiovascular safety of linagliptin. These 2 CV outcome trials were conducted in T2DM patients at elevated or high CV risk thus representative of a population frequently encountered in clinical practice. Considering the substantial additional data provided from CARMELINA and CAROLINA, the fact that results from these trials, including subgroup analysis of patients in risk categories reflecting existing vascular disease did not show any increased risk of adverse CV events with linagliptin, BI proposes to remove 'patients with a history of cardiovascular events' as missing information.

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

SVII.3.1 Presentation of important identified risks and important potential risks

An overview of the safety analysis sets used for the characterisation of risks is given in SVII.Table 21.

In this RMP update, individual trial data from 1218.74, (CAROLINA) a CV safety study have been added for the following safety topics described below.

- Pancreatitis
- Pancreatic cancer
-

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SVII.Table 21 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 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.	N/A	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

The TS, which was the basis for all efficacy and safety analyses in the CAROLINA study included 6033 patients. Of these, 19 treated patients participated at more than 1 site. These 19 "duplicate patients" were excluded from the TS to result in the TS_D as indicated by the "D" in the name of the analysis set. The 19 patients excluded from the TS_D were balanced between the treatment groups, with 9 in the linagliptin group and 10 in the glimepiride group. The remaining 6014 patients in the TS_D included 3000 patients treated with glimepiride and 3014 patients treated with linagliptin. All SAEs and adjudication trigger events for the duplicate patients were consolidated and included in the TS. Where data from these 19 duplicate patients were not included, this is indicated as analysed based on the TS_D.

SVII.3.1.1 Important identified risk: Pancreatitis

Pancreatitis was assessed as an AE of special interest in the clinical trial programme of linagliptin monotherapy based on US FDA recommendations following review of other DPP-4 inhibitors.

Pancreatitis was defined as an important identified risk based on cases of pancreatitis that have been identified as side effects associated with other DPP-4 inhibitors [R09-5798] and the observation of cases of pancreatitis within the linagliptin monotherapy clinical development programme.

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SVII.3.1.1.1 Potential mechanisms

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.3.1.1.2 Evidence source and strength of evidence

In clinical trials, pancreatitis occurred more frequently in patients treated with linagliptin than in those treated with either comparators (active substances used as a reference) or placebo (dummy with no active therapeutic effect).

SVII.3.1.1.3 Characterisation of the risk

Clinical trial data
Patients with pancreatitis were identified using the narrow SMQ 'pancreatitis' (20000022), plus the MedDRA PT 'pancreatitis chronic' (10033649). In the CARMELINA and CAROLINA trials, pancreatic events 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 type 2 diabetes mellitus (SAF-2)

SVII.Table 22 shows an overview of pancreatitis (SAF-2). Pancreatitis was reported infrequently in SAF-2, but at a slightly higher rate in the linagliptin group than in the placebo group. In the linagliptin arm, most events of pancreatitis were mild or moderate in intensity whereas in the placebo arm, most were severe. The majority of outcomes were reported as "recovered" (in both treatment arms). There were no fatal events of pancreatitis.

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SVII.Table 22 Overview on pancreatitis (SAF-2)

	Placebo	Linagliptin
Number of patients treated, N (%)	4936 (100.0)	7136 (100.0)
Total overall time at risk (PY)	3211.82	4170.81
Patients with pancreatitis, N (%)	4 (0.1)	8 (0.1)
95% CI	[0.0, 0.2]	[0.1, 0.2]
Rate/100 PY	0.12	0.19
Incidence rate ratio[1], (95% CI)	1.85 [0.5, 6.3]	
Incidence risk ratio[1], (95% CI)	1.88 [0.6, 6.4]	
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 (0.0)	1 (12.5)
Outcome[2,4], N (%)		
Recovered	4 (100.0)	7 (87.5)
Sequelae	0 (0.0)	1 (12.5)
Intensity[2], N (%)		
Mild	0 (0.0)	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]Each of the outcomes could be individually assigned to an event, i.e. fatal would not be a subset of not recovered

Data source: data on file: 8-05-output-rmp-2017-final, Table 7.2.4

Trial 1218.22 (CARMELINA)

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 (data source, 1218.22 CTR [c22196815-02], Table 15.3.1.5.3).

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SVII.Table 23 Patients with CECP-confirmed pancreatitis by treatment - 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: 1218.22 CTR [c22196815-02], 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).

Trial 1218.74 (CAROLINA)

Pancreatitis events were adjudicated by the independent CECP. Frequencies of patients with CECP-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. 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: 1218.74 CTR [c23238241-01], Table 12.1.4.5: 1).

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SVII.Table 24 Patients with CECP-confirmed pancreatitis by treatment - 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: 1218.74 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 an acute pancreatitis was similar for patients in both treatment groups (p=0.85) (Data source: 1218.74 CTR [c23238241-01], Figure 15.3.1.5: 1 and Table 15.3.1.5: 4).

Conclusion on clinical data
Overall, the findings for pancreatitis are consistent with previous safety information for linagliptin.

SVII.3.1.1.4 Risk factors and risk groups

Patients with T2DM have an increased risk for pancreatitis. Further, obesity, history of alcohol use, history of smoking, higher comorbidity index, hypertriglyceridaemia, and any history of gallbladder disease are important risk factors of acute pancreatitis [R10-6279, R10-6620, R10-5391].

Results of a retrospective cohort study using data from 2007 to 2009 of a large US medical and pharmacy claims database also show a higher percentage of biliary stone disease and hypertriglyceridaemia among patients with diabetes compared to patients without diabetes. Biliary stone disease was diagnosed in 0.84% of the diabetics compared to 0.60% in the non-diabetics ($p<0.0001$). The respective numbers for hypertriglyceridaemia were 1.71% vs. 0.95% ($p<0.0001$) [R10-5391].

SVII.3.1.1.5 Preventability

The preventability of pancreatitis with linagliptin treatment is unknown. To mitigate for the risk of pancreatitis, the topic is addressed in the EU SmPC section 4.4 (special warnings and precautions for use).

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SVII.3.1.1.6 Impact on the risk-benefit balance of the product

Pancreatitis can lead to hospitalisation and can be potentially life-threatening in some cases. Treatment with linagliptin should be discontinued. Most patients with pancreatitis recover with adequate treatment.

SVII.3.1.1.7 Public health impact

Symptoms of pancreatitis may interfere with daily activities or lead to hospitalisation.

SVII.3.1.2 Important potential risk: 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). This topic has been under close surveillance for Trajenta.

SVII.3.1.2.1 Potential mechanisms

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 AR. Therefore, the different levels of the cell-surface CD26-ADA complex and relative expression of ARs 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

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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].

SVII.3.1.2.2 Evidence source and strength of evidence

Pancreatic cancer was added as an important potential risk at the request of the CHMP in the EMA. Recently completed CV outcome trials 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 treated group.

SVII.3.1.2.3 Characterisation of the risk

Clinical trial 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 type 2 diabetes mellitus (SAF-2)

SVII.Table 25 provides an overview on pancreatic cancer (SAF-2). Of the 2 patients retrieved in the search with pancreatic cancer only 1 had an event of Pancreatic carcinoma stage II; the other patient had an event of pancreatic cyst that was retrieved due to the search parameters. Both of these patients were in the linagliptin treatment arm.

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SVII.Table 25 Overview on pancreatic cancer (SAF-2)

	Placebo		Linagliptin
Number of patients treated, N (%)	4936 (100.0)		7136 (100.0)
Total overall time at risk (PY)	3211.95		4173.69
Patients with pancreatic cancer, N (%)	0		2 (0.0)
95% CI	N/A		[0.0, 0.1]
Rate/100 PY	0.00		0.05
Incidence rate ratio[1], (95% CI)		N/A	
Incidence risk ratio[1], (95% CI)		N/A	
Seriousness[2,3], N (%)	0		1 (50.0)
Required hospitalisation	0		1 (50.0)
Outcome[2,4], N (%)			
Recovered	0		1 (50.0)
Not yet recovered	0		1 (50.0)
Intensity[2], N (%)			
Mild	0		1 (50.0)
Moderate	0		1 (50.0)

[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]Each of the outcomes could be individually assigned to an event, i.e. fatal would not be a subset of not recovered.

Data source: data on file, 8-05-output-rmp-2017-final, Table 7.2.9

Trial 1218.22 (CARMELINA)

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: data on file, 1218.22 CTR [c22196815-02], 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: data on file, 1218.22 CTR [c22196815-02], 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, 1218.22 CTR, Listing 16.2.7.9).

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Trial 1218.74 (CAROLINA)
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: data on file, 1218.74 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 1218.22 and 1218.74.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.

Post-marketing data
A cumulative search was conducted up to 02 May 2018 for reports associated with Trajenta from post-marketing sources (excluding clinical trials). This search for potential events of 'pancreatic cancer' using the narrow BIcMQ 'pancreatic neoplasms' (MedDRA version 20.1) retrieved 89 cases for Trajenta including 8 cases that contained the non-specific PT 'pancreatic cyst'.

The most commonly reported PT (in 78.7% of cases) was 'pancreatic carcinoma'. 95.5% of the cases were serious and 23 events (in 23 cases), or 25.8% of cases overall, were reported with fatal outcome.

Notably, 30.3 % of the cases had TTO <366 days. In 21 cases the TTO was more than 1 year; 1 of these cases involved benign neoplasms and 1 was a non-serious case of pancreatic cyst. The remaining 18 cases with TTO >1 year were reviewed in detail. In cases where sufficient information was available for assessment, concomitant malignancies, positive family history of cancer, history of exposure to chemical carcinogens, and risk factors such as smoking, excessive alcohol consumption, and obesity were confounding factors that could plausibly be linked to the event, but none of the cases provided evidence of a causal association with Trajenta. It should be noted that, in the context of the cumulative exposure of 10 414 600 PY, 89 cases reported for Trajenta results in a reporting rate of <0.1 per 10 000 PY.

Overall, the cumulative review of post-marketing cases did not identify a new safety concern or change in the understanding of the risk of 'pancreatic cancer'.

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SVII.3.1.2.4 Risk factors and risk groups

Pancreatic cancer classically presents late in life, and has a poor prognosis and rapid clinical course. The risk factors are complex and work is still ongoing in identifying risk factors and their impact on the risk of developing pancreatic cancer. The current identified and potential risk factors are summarised below [R13-2887].

Identified risk factors for pancreatic cancer

- Smoking (in which a dose response relationship has been observed)
- Obesity
- Family history
- Genetic factors including mutations in breast cancer 2 (BRCA2), CDKN2A gene (familial atypical multiple mole-melanoma [FAMMM] syndrome), STK11 (Peutz-Jeghers Syndrome), PRSS1 (hereditary pancreatitis), MLH1 or MSH2 (hereditary non-polyposis colorectal cancer [HNPCC] or Lynch syndrome)
- Non-O blood groups (the significance of this is still unknown)
- Chronic Infections, e.g. hepatitis B virus, hepatitis C virus, Helicobacter pylori
- Surgery, e.g. cholecystectomy, partial gastrectomy
- Pancreatitis and chronic pancreatitis (familial & tropical pancreatitis appears to show this more strongly)

Potential risk factors for pancreatic cancer (as some studies have shown a relationship and some have not, there is an unknown relationship)

- Alcohol consumption
- Sunlight & vitamin D
- Diabetes
- Consumption of red and processed meat
- Other medical conditions that may increase risk include cystic fibrosis & periodontal disease (the cystic fibrosis gene is also associated with pancreatitis; it is not clear if this association with pancreatic cancer is due to the pancreatitis being a risk for cancer or cystic fibrosis being a risk in its own right)

Previous suspected associations, which now seem to be disregarded

- Caffeine (found to not have an association in a recent meta-analysis)

Considering patients with pancreatic cancer, at diagnosis about 25% have diabetes mellitus, and roughly another 40% have pre-diabetes (higher than normal blood glucose levels). Compared with non-diabetic individuals, patients with long-term (≥5 years) T2DM have a

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50% increased risk of pancreatic cancer. Pancreatic cancer can cause diabetes, and sometimes diabetes is an early sign of the tumour so the observed data can be difficult to interpret: Do patients with diabetes have a higher risk of cancer or is this confounded by the proportion of the diabetic patients who develop pancreatic cancer whose diabetes is caused by pancreatic failure associated with the clinically undetected cancer? Elevated pancreatic cancer risk has also been reported among individuals with type-I diabetes. Recent reports also suggest that hyperglycaemia, abnormal glucose metabolism and insulin resistance are associated with increased risk of pancreatic cancer [R13-2887].

SVII.3.1.2.5 Preventability

Families of patients with a high risk of developing pancreatic cancer, for example, patients with hereditary chronic pancreatitis, have been closely followed. To date, no preventive therapies for pancreatic cancer have been identified.

SVII.3.1.2.6 Impact on the risk-benefit balance of the product

Pancreatic cancer is a serious condition, which may be life-threatening or even fatal; and requires hospitalisation and dedicated treatment. The available data is not conclusive of an increased risk of pancreatic cancer with linagliptin.

SVII.3.1.2.7 Public health impact

Pancreatic cancer may interfere with daily activities or lead to hospitalisation. The impact of a theoretical risk of pancreatic cancer being causally associated with Trajenta or Jentadueto is not possible to calculate using present data; however, it is likely to be very low. Pancreatic cancer presents late in life and with few early symptoms. Thus, it is not uncommon at presentation for the cancer to be inoperable and the disease often has a rapid progression. A fatal outcome is inevitable with present oncological therapies.

SVII.3.2 Presentation of the missing information

SVII.3.2.1 Missing information: Pregnant or breast-feeding women

SVII.3.2.1.1 Evidence source

Animal reproduction studies 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.

There was no indication of a teratogenic effect attributable to the co-administration of linagliptin+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

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maximum recommended human dose), teratogenicity of metformin was observed [U10-2386-01].

A cumulative search for 'drug exposure during pregnancy' in the BI GDSS up to 02 May 2018 was conducted using MedDRA version 20.1. 36 cases from all sources were identified where DEDP was reported in patients treated with linagliptin, linagliptin+metformin, or linagliptin+empagliflozin in the linagliptin clinical development programme and from the post-marketing sources.

Of the 36 cases, 13 cases were from clinical trials, 2 cases were from observational studies, and 21 cases were spontaneous. Pregnancy outcome, available in 15 of the 36 cases, was normal birth in 4 cases, and abnormal in 11 cases. Pregnancy outcome was not yet known in the remaining 21 cases. Available information on pregnancies with abnormal outcome is summarised in the table below. No cases of breast feeding on Trajenta were reported to date.

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SVII.Table 26 Cumulative summary of DEDP cases for Trajenta and Jentadueto (excluding cases with normal outcomes)

Case No.	Clinical trial / PM source	Drug exposure	Time of exposure (Trimester)	Pregnancy outcome
1	CT	Linagliptin 5mg	1	Large for date baby, male
2	CT	Linagliptin 5mg	1	Premature, male (gestational age 31 weeks), patent ductus arteriosus and a single umbilical artery
3	CT	Free combination linagliptin 2.5mg and metformin 1000 mg.	1	Induced abortion
4	CT	Linagliptin 5mg	1	Still birth, abrupted placenta, ruptured uterus
5	CT	Free combination linagliptin 5mg daily+metformin 2000mg daily	1	Holoprosencephaly diagnosed intrauterine, at gestational age 19.4 weeks. Induced abortion
6	CT	Free combination linagliptin 5mg, metformin 500mg q.d.	1	Induced abortion (due to absence of embryonic heart beat)
7	SP	Linagliptin unk dose	Unk	Foetal death at 22 weeks of gestation (twin pregnancy)
8	CT	Unblinded to linagliptin 5mg.	1	Abortion spontaneous
9	CT	Unblinded to empagliflozin +linagliptin	1	Abortion induced
10	CT	Fixed dose combination Linagliptin 2.5 mg/ Metformin 500mg	1	Induced abortion
11	SP	Trajenta, 5mg	1	Abortion spontaneous

Data source: BI GDSS, status 02 May 2018.

As a precaution, women should not be treated with Trajenta or Jentadueto during pregnancy or breast-feeding. No new safety concern was identified from cumulative or interval reviews of DEDP or drug exposure during breast-feeding cases. No additional pharmacovigilance activities or risk minimisation measures are planned for this safety concern. The labelling in section 4.6 “Fertility, Pregnancy, and Lactation” of the current EU SmPCs for Trajenta and Jentadueto is considered appropriate to provide information on this topic.

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SVII.3.2.1.2 Anticipated risk/consequence of the missing information

A theoretical risk for the unborn or breast-fed child exists. As a precaution, it is preferable to avoid the use of linagliptin during pregnancy. Linagliptin should not be used by breast-feeding women.

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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
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

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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

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MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

SVIII.Table 1 Summary of safety concerns

Important identified risks	Pancreatitis
Important potential risk	Pancreatic cancer
Missing information	Pregnancy/breast-feeding

SVIII.1 REFERENCES

Not applicable

ABBREVIATIONS

Not applicable

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

PART III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for malignancy/neoplasm
A questionnaire to collect standardised data to follow-up on events of pancreatic cancer is used for all spontaneous case reports where such an event has been reported (Appendix 4). The questionnaire collects information on diagnosis, cytology or biopsy results, staging of the neoplasm, types of tests performed (e.g. genetic analysis, bone marrow aspiration) and results of any such tests performed, and relevant patient medical history.

Specific adverse reaction follow-up questionnaires for pancreatitis
A questionnaire to collect standardised data to follow-up on events of pancreatitis is used for all spontaneous case reports where such an event has been reported (Appendix 4). The questionnaire collects information on prior history of pancreatitis, elevated amylase or lipase, and other relevant medical history such as gallstones, other gastrointestinal history, and alcohol use. The questionnaire also collects details on symptoms reported, any relevant laboratory analyses, and imaging results if available.

PART III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities are considered sufficient to address all safety concerns with the aim to get and analyse relevant safety data from post-marketing experience to fully assess the safety of the product.

PART III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no ongoing or planned additional pharmacovigilance activities.

PART III.4 REFERENCES

Not applicable

ABBREVIATIONS

MI	Myocardial infarction
OAD	Oral antidiabetic (medication)
T2DM	Type 2 diabetes mellitus

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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.

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PART V RISK MINIMISATION MEASURES

RISK MINIMISATION PLAN

The routine risk minimisation measures described in this section apply to both Trajenta and to Jentadueto, unless otherwise specified.

PART V.1 ROUTINE RISK MINIMISATION MEASURES

PV.Table 1 Description of routine risk minimisation measures by safety concern (Pancreatitis – important identified risk)

Safety concern	Routine risk minimisation activities
Pancreatitis	*Routine risk communication* SmPC sections 4.4 and 4.8 PL sections 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Trajenta and Jentadueto are available by prescription only

PV.Table 2 Description of routine risk minimisation measures by safety concern (Pancreatic cancer – important potential risk)

Safety concern	Routine risk minimisation activities
Pancreatic cancer	*Routine risk communication* None *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Trajenta and Jentadueto are available by prescription only

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PV.Table 3 Description of routine risk minimisation measures by safety concern (Pregnancy/breast-feeding – missing information)

Safety concern	Routine risk minimisation activities
Pregnancy/breast-feeding	*Routine risk communication* SmPC Section 4.6 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Trajenta and Jentadueto are available as prescription-only medications

PART V.2 ADDITIONAL RISK MINIMISATION MEASURES

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

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PART V.3 SUMMARY OF RISK MINIMISATION MEASURES

PV.Table 4 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Pancreatitis	*Routine risk minimisation measures:* • SmPC sections 4.4 and 4.8 • PL sections 2 and 4 • Available by prescription only *Additional risk minimisation measures:* • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* • Adverse reaction follow-up questionnaire *Additional pharmacovigilance activities*: • None
Important potential risk		
Pancreatic cancer	*Routine risk minimisation measures:* • Available by prescription only *Additional risk minimisation measures:* • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* • Adverse reaction follow up questionnaire *Additional pharmacovigilance activities:* • None
Missing information		
Pregnancy/breast-feeding	*Routine risk minimisation measures:* • • SmPC Section 4.6 • • PL Section 2 • • Available by prescription only *Additional risk minimisation measures:* • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* • None *Additional pharmacovigilance activities:* • None

PART V.4 REFERENCES

Not applicable

ABBREVIATIONS

PL	Package leaflet
SmPC	Summary of Product Characteristics

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PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

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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. The RMP details important risks of Trajenta and Jentadueto, how these risks can be minimised, and how more information will be obtained about Trajenta's and Jentadueto's risks and uncertainties (missing information).

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 or changes to the current ones 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

Important risks of Trajenta and Jentadueto, together with measures to minimise such risks and the proposed studies for learning more about their risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

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In the case of Trajenta and Jentadueto, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

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

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

II.A List of important risks and missing information

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

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Table 1 List of important risks and missing information

Important identified risks	Pancreatitis
Important potential risks	Pancreatic cancer
Missing information	Pregnancy/breast-feeding

II.B Summary of important risks

Table 2 Important identified risks

Pancreatitis	
Evidence for linking the risk to the medicine	In clinical trials, pancreatitis occurred more frequently in patients treated with linagliptin than in those treated with either comparators (active substances used as a reference) or placebo (dummy with no active therapeutic effect).
Risk factors and risk groups	Patients with T2DM have an increased risk for pancreatitis. Further, obesity, history of alcohol use, history of smoking, higher comorbidity index, hypertriglyceridaemia, and any history of gallbladder disease are important risk factors of acute pancreatitis (see also Section SVII.3.1.1.4). Results of a retrospective cohort study using data from 2007 to 2009 of a large US medical and pharmacy claims database also show a higher percentage of biliary stone disease and hypertriglyceridaemia among patients with diabetes compared to patients without diabetes. Biliary stone disease was diagnosed in 0.84% of the diabetics compared to 0.60% in the non-diabetics ($p<0.0001$). The respective numbers for hypertriglyceridaemia were 1.71% vs. 0.95% ($p<0.0001$).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 • Available by prescription only Additional risk minimisation measures: None

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Table 3 Important potential risk

Pancreatic cancer	
Evidence for linking the risk to the medicine	Pancreatic cancer was added as an important potential risk at the request of the CHMP in the EMA. Recently completed CV outcome trials for 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.
Risk factors and risk groups	Pancreatic cancer classically presents late in life, and has a poor prognosis and rapid clinical course. The risk factors are complex and work is still ongoing in identifying risk factors and their impact on the risk of developing pancreatic cancer. The current identified and potential risk factors are summarised below. *Identified risk factors for pancreatic cancer* • Smoking (in which a dose response relationship has been observed) • Obesity • Family history • Genetic factors including mutations in breast cancer 2 (BRCA2), CDKN2A gene (familial atypical multiple mole-melanoma [FAMMM] syndrome), STK11 (Peutz-Jeghers Syndrome), PRSS1 (hereditary pancreatitis), MLH1 or MSH2 (hereditary non-polyposis colorectal cancer [HNPCC] or Lynch syndrome) • Non-O blood groups (the significance of this is still unknown) • Chronic Infections, e.g. hepatitis B virus, hepatitis C virus, Helicobacter pylori • Surgery, e.g. cholecystectomy, partial gastrectomy • Pancreatitis and chronic pancreatitis (familial & tropical pancreatitis appears to show this more strongly) *Potential risk factors for pancreatic cancer (as some studies have shown a relationship and some have not, there is an unknown relationship)* • Alcohol consumption • Sunlight & vitamin D • Diabetes

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Table 3 (cont'd) Important potential risk

Pancreatic cancer (cont'd)	• Consumption of red and processed meat
Risk factors and risk groups (cont'd)	• Other medical conditions that may increase risk include cystic fibrosis & periodontal disease (the cystic fibrosis gene is also associated with pancreatitis; it is not clear if this association with pancreatic cancer is due to the pancreatitis being a risk for cancer or cystic fibrosis being a risk in its own right) *Previous suspected associations, which now seem to be disregarded* • Caffeine (found to not have an association in a recent meta-analysis) Considering patients with pancreatic cancer, at diagnosis about 25% have diabetes mellitus, and roughly another 40% have pre-diabetes (higher than normal blood glucose levels). Compared with non-diabetic individuals, patients with long-term (≥5 years) T2DM have a 50% increased risk of pancreatic cancer. Pancreatic cancer can cause diabetes, and sometimes diabetes is an early sign of the tumour so the observed data can be difficult to interpret: Do patients with diabetes have a higher risk of cancer or is this confounded by the proportion of the diabetic patients who develop pancreatic cancer whose diabetes is caused by pancreatic failure associated with the clinically undetected cancer? Elevated pancreatic cancer risk has also been reported among individuals with type-I diabetes. Recent reports also suggest that hyperglycaemia, abnormal glucose metabolism and insulin resistance are associated with increased risk of pancreatic cancer.
Risk minimisation measures	Routine risk minimisation measures: • Available by prescription only Additional risk minimisation measures: None

Table 4 Missing information

Pregnancy/breast-feeding	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 • PL Section 2 • Available by prescription only Additional risk minimisation measures: None

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II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligations of Trajenta or Jentadueto.

II.C.2 Other studies in post-authorisation development plan

None

ABBREVIATIONS

CV	Cardiovascular
DPP-4	Dipeptidyl peptidase-4
EMA	European Medicines Agency
EPAR	European Public Assessment Report
PL	Package leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
T2DM	Type 2 diabetes mellitus

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APPENDIX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

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APPENDIX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS **140**

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Malignancy and Neoplasm Questionnaire **142**

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Malignancy and Neoplasm Questionnaire

Trial Number: Patient Number: Center Number:

BI Case ID (filled out by BI):

Dear Health Care Provider,

Thank you for bringing this event to our attention. In order to fully understand the event, we would like to ask you for a few details. In answering the questions below, you will allow Boehringer Ingelheim to keep the safety information for physicians and patients accurate.
Thank you for your help.

Description of the Malignancy /Neoplasm Event:

Diagnosis:

Date (dd/mm/yyyy):

Cytology or Biopsy:
(site(s) and results including histological typing of tumor and immunophenotyping if appropriate. Please provide copy of pathology report, lymph node biopsy or an English summary as well as gene rearrangement studies if performed)

Date (dd/mm/yyyy):

Staging of the Neoplasm: T N M

Were any of the following tests performed? Please check all that apply and specify which test(s), with date and result.

☐ Genetic analysis for known mutations associated with malignancy: Date
Result:

☐ Bone marrow aspiration ☐ yes ☐ no, If "yes" Date
Result:

☐ Complete Blood Count Date
Result:

☐ Biomarkers (e.g. PSA, AFP, CA19.9, HER-2, etc.) Date
Result:

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Boehringer Ingelheim

Malignancy and Neoplasm Questionnaire

☐ Imaging tests (e.g. X-ray, CT scan, MRI, PET Scan, Mammogram) Date

Result:

☐ Postoperative pathology results Date

Result:

Patient Medical History:

Does the patient have a history of any of the following prior to the start of the suspect drug? Please check all fields that apply and provide details as applicable.

☐ Infection (e.g., HIV, HCV, HPV)
☐ Personal History of Malignancy
☐ Family History of Malignancy
☐ Immunosuppressive Condition (incl. therapeutic)
☐ Alcohol Abuse
☐ UV exposure, PUVA/UVB
☐ Exposure to Ionizing Radiation
☐ History of Radioiodine Exposure
☐ Smoking or Tobacco Chewing
☐ Type 3c Diabetes Mellitus

☐ History of Treatment with Pancreatic Enzymes
☐ Previous Colonoscopy
☐ Previous PSA
☐ Previous Chest X-Ray
☐ Previous Mammogram

Any further information:

Reporter's name:

Date (dd/mm/yyyy):

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

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