EU Risk Management Plan for Jardiance (empagliflozin)

RMP version to be assessed as part of this application:

RMP version number:	21.1
Data lock point for this RMP:	09 Sep 2022
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Rationale for submitting an updated RMP:	Consolidation of v20.1 (current EMA approved version) and v21.0 (new indication paediatric T2DM indication)
Summary of significant changes in this RMP:	V21.0 *New indication* - Update of Module SI to include the epidemiology of the proposed indication - Update of the clinical trial exposure tables in Modules SIII to include data from the DINAMO trial (1218-0091) - Update of the exclusion criteria in Module SIV with the DINAMO trial (1218-0091) - Update of the risk characterisation section in Module SVII to include risk analyses from the DINAMO trial (1218-0091) - Update of Part VI with the new proposed indication *Other* Administrative updates (Part I, Appendix 8)

Other RMP versions under evaluation:

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Details of the currently approved RMP:	
Version number:	20.1
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Date of approval (opinion date):	24 Jul 2023
QPPV name:	Sven Kohler
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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PART I PRODUCT OVERVIEW

PI.Table 1 Product Overview

Active substance (INN or common name)	Empagliflozin (empagliflozin)
Pharmacotherapeutic group (ATC code)	SGLT-2 inhibitor (A10BK03)
Marketing Authorisation Holder	Boehringer Ingelheim International GmbH
Medicinal product to which this RMP refers	1
Invented name in the EEA	Jardiance
Marketing authorisation procedure	Centralised
Brief description of the product	*Chemical class* SGLT-2 inhibitor
	Summary of mode of action T2DM Empagliflozin is a selective inhibitor of SGLT-2. SGLT-2 is expressed in the renal proximal tubes and transports glucose across the membrane against a concentration gradient, accounting for about 90% of the total renal glucose re-absorption. Inhibition of SGLT-2 decreases the renal re-absorption of glucose, thereby increasing urinary glucose excretion and lowering plasma glucose levels. In addition, the calorie loss associated with the increased glucose excretion may result in weight loss. Further, SGLT-2 inhibitors may reduce blood pressure, possibly via a mild diuretic effect.

PI.Table 1 (cont'd) Product Overview

	Summary of mode of action (cont'd) Heart failure and chronic kidney disease Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, increasing tubuloglomerular feedback and reducing intraglomerular pressure, lowering both pre- and afterload of the heart, downregulating sympathetic activity, and reducing left ventricular wall stress as evidenced by lower NT-proBNP values which may have beneficial effects on cardiac remodelling, filling pressures and diastolic function as well as preserving kidney structure and function. Other effects like an increase in haematocrit, a moderate reduction in body weight and blood pressure may further contribute to the beneficial cardiac and renal effects.
	Important information about its composition Not applicable
Hyperlink to the Product Information	Product information
Indications in the EEA	*Current* Jardiance is indicated for the treatment of adults and children aged 10 years and above with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise • as monotherapy when metformin is considered inappropriate due to intolerance • in addition to other medicinal products for the treatment of diabetes For study results with respect to combinations, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see SmPC sections 4.4, 4.5, and 5.1. Jardiance is indicated in adults for the treatment of symptomatic chronic heart failure. Jardiance is indicated in adults for the treatment of chronic kidney disease.
	Proposed Not applicable

PI.Table 1 (cont'd) Product Overview

Dosages in the EEA	*Current* T2DM (adults and children aged 10 years and above): 10 mg and 25 mg, once daily HF: 10 mg, once daily CKD: 10 mg, once daily
	Proposed Not applicable
Pharmaceutical form and strengths	*Current* T2DM (adults and children aged 10 years and above): Film-coated tablet, 10 mg and 25 mg HF: Film-coated tablet, 10 mg CKD: Film-coated tablet, 10 mg
	Proposed Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

ABBREVIATIONS

ATC	Anatomical therapeutic chemical
CKD	Chronic kidney disease
EEA	European Economic Area
EU	European Union
HF	Heart failure
INN	International non-proprietary name
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
RMP	Risk Management Plan
SGLT-2	Sodium-dependent glucose co-transporter 2
SmPC	Summary of Product Characteristics
T2DM	Type 2 diabetes mellitus

PART II SAFETY SPECIFICATION

MODULE SI EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATIONS

SI.1 CHRONIC KIDNEY DISEASE

SI.1.1 Incidence

Recent data on incidence of CKD are sparce. Among available studies, populations vary according to age, comorbid conditions, and CKD stage. Metrics used to characterise incidence also vary depending on data source. Therefore, CKD incidence estimates presented should be compared with caution considering the exact methodology used and populations examined.

A prospective cohort study in a community-based sample of 4409 individuals in the urban community of greater Nancy, France [R22-3501] reported the annual incidence rate of stage 3 to 5 CKD at 977.7 per 1 million population. A similar prospective study reported estimates based on data from 3443 outpatients with T2DM sampled from 56 primary health care centres in Madrid, Spain [R22-3448]. The cumulative incidence of CKD at 5 years was 10.23% (95% CI 9.12, 11.43) and the incidence density was 2.07 (95% CI 1.83, 2.33) cases per 1000 patient-months or 2.48 (95% CI 2.19, 2.79) cases per 100 PY. 2 retrospective studies were also identified, including an investigation conducted among adults with stage 3-4 CKD and ≥3 visits to a primary care clinician in Alberta, Canada [R22-3566]. Cumulative CKD incidence of 2.4% (89 485 of 3 682 277 individuals) for stage 3 to 4 CKD was reported across a 3-year period. A similar retrospective cohort study examined data from a primary care EHR database and reported the incidence rate of CKD in adults was 1213 per 100 000 PY.

Additional studies are available reporting incidence of ESRD only (not including the less advanced stages of CKD), however, these studies were not included in this review since the target population does not include patients classified as ESRD.

SI.Table 1 Available data on incidence rates of CKD published between 2014 and 2022 in Canada, Europe, and the US

Reference	Country	Time Period	Data source	Sample size, n	Age, years	Incidence
van Blijderveen 2014 [R22-3454]	The Netherlands	1994-2011	EMRs of a group of 150 GPs	784 563 adults	≥20 Median (IQR): 44.4 (31.7-59.2)	Overall per 1000 PY (95% CI): 4.79 (4.70-4.89) Stage 1: 0.60 Stage 2: 0.05 Stage 3: 3.70 Stage 4: 0.25 Stage 5: 0.18
Ayav 2016 [R22-3501]	France	2004-2006	Prospective observational cohort	Followed for CKD incidence: 4409	Mean (SD): 76.0 (13.0)	CKD: 977.7 (902.9-1057.0)[1]
Chong 2022 [R22-3566]	Canada	April 2011-March 2014	Alberta Kidney Disease Network	Stage 3a: 51 916 Stage 3b: 26 418 Stage 4: 8141	Mean (SD) Poor care continuity: 76.1 (12.6) Moderate care continuity: 75.7 (11.4) High care continuity:76.2 (10.5) Overall: 76.0 (11.2)	Incidence of CKD stage 3 to 4 diagnosis: 89 485/3 682 277 (2.4%)
Population with diabetes						
Salinero-Fort 2015 [R22-3448]	Spain	2007-2012	MADIABETES study	2620 patients with T2DM	Mean (SD): 67.3 (10.8)	5-Year cumulative incidence stage 3-5: 10.23% (95% CI 9.12, 11.43) Incidence density: 2.07 (95% CI 1.83, 2.33) cases per 1000 patient-months or 2.48 (95% CI 2.19, 2.79) cases per 100 PY

[1]Reported as per million population

SI.1.2 Prevalence

CKD is a growing pandemic which affects approximately 700 million people worldwide [R22-0692]. Several recent studies are available reporting prevalence of CKD in various geographic regions; however, populations vary according to age, comorbid conditions, and CKD stages examined. Metrics used to characterise prevalence also vary across studies. Therefore, CKD prevalence estimates presented should be compared with caution considering the study methodology used and populations examined.

Contemporary population-based studies suggest the overall prevalence of CKD as measured by percentage ranged from 3% to 36.5% depending on region, population, data source, and/or method used to identify CKD patients [SI.Table 2]. The GBD study reported a global age-standardised prevalence rate of 8724 per 100 000 in 2017 and the prevalence for all CKD stages was 9.1%; 5.0% for stage 1 or 2, 3.9% for stage 3, 0.16% for stage 4, and 0.07% for stage 5 [R22-0692]. Age-standardised prevalence of stage 3 to 5 CKD in 2016 ranged from 5.5% to 10.4% in high income regions, 7.6% to 13.1% in Central and Eastern Europe, and 7.4% to 13.1% in other regions [R22-3578].

In North America, results from a Canadian registry indicate that from 2010-2015, the overall prevalence of CKD stages 3a to 5 was 71.94 per 1000 individuals [R22-3571]. A retrospective study of nearly 150 000 patients in an integrated healthcare delivery system in the US (Kaiser Permanente Northwest) reported that approximately 14.5% of adults had stages 1 to 5 CKD [R20-4014]. 2 recent UK studies [R22-3567, R22-3459] reported a prevalence of CKD stages 3 to 5 as 2.6% and 3.3% [R22-3568].

In Japan, a registry study [R22-3572] reported that among individuals at high risk for CKD (i.e. reported history of hypertension or diabetes or family history of hypertension, diabetes, or CKD), prevalence of CKD was 26.5% among KEEP patients compared to 13.8% of non-KEEP patients. A Chinese study [R22-3726] utilising 3 national databases and found that 4.8% of hospitalised individuals had CKD based on ICD-10 codes.

In Australia, a report based on data from the National Health Measures survey [R22-3590] reported an age-standardised prevalence of self-reported CKD of 10.7% (95% CI 9.9, 11.6%).

SI.Table 2 Summary of estimates of CKD prevalence published between 2014 and 2022 in Europe and the US

Reference	Country/ Region	Time Period	Data source(s)	Sample size, n	Age, years	CKD Prevalence Estimate(s)
AIHW 2020 [R22-3590]	Australia	2011-2012	National Health Survey	868 000	18+	Age-standardised (95% CI): Overall: 10.0% (9.2-10.8%) - Men: 11.1% (9.9-12.4%) - Women: 10.4% (9.1-11.6%) Crude: - Stage 1: 4.3% (3.6-4.9%) - Stage 2: 2.7% (2.3-3.1%) - Stage 3a: 3.0% (2.6-3.4%) - Stage 3b-5: 1.0% (0.7-1.3%)
van Blijderveen 2014 [R22-3454]	The Netherlands	1994-2011	EMRs of a group of 150 GPs	784 563 adults	≥20 years; Mean (IQR) at the start of follow-up: 44.4 (31.7-59.2)	% (95% CI) Possible CKD: 6.7% (6.6-6.7%) Definite CKD: 5.1% (5.1-5.1%) - Stage 1: 0.32% - Stage 2: 0.03% - Stage 3: 4.17% - Stage 4: 0.38% - Stage 5: 0.15%

SI.Table 2 (cont'd) Summary of estimates of CKD prevalence published between 2014 and 2022 in Europe and the US

Carpio 2022 [R22-3567]	UK	1990-2013	Cross-sectional study	286 162 patients without diabetes	Age, n (%), reported as CKD+HTN/CKD-HTN: - <50 years: 346 (8.4) / 720 (27.1) - 50-59 years: 568 (13.8) / 642 (24.2) - 60-69 years: 620 (15.0) / 480 (18.1) - 70-79 years: 1127 (27.3) / 406 (15.3) - 80-89 years: 1149 (27.8) / 322 (12.1) - >90 years: 321 (7.8) / 87 (3.3)	CKD stages 3-5: 3.3%
MacRae 2021 [R22-3459]	UK (Scotland)	2007	Cross-sectional study/survey	28 489	Mean (SD): All CKD: 74.8 (12.3) - Stage 3a: 73.1 (12.2) - Stage 3b: 79.4 (10.9 - Stage 4: 78.2 (13.0) - Stage 5: 72.3 (14.4)	CKD stages 3-5: 2.6%
Bello 2019 [R22-3571]	Canada	2010-2015	Cross-sectional study/survey	559 475	Mean (SD): 48.5 (17.8)	Prevalence by stage per 1000, 2010–2015: - 3a: 31.8 - 3b: 25.3 - 4: 11.7 - 5: 3.3 Overall: 71.9
Al Kibria 2020 [R22-3198]	United States	2015-2018	NHANES	1814	20+ y Mean (SD): 61 (17.3)	Any CKD stage: 13.3% (95% CI 12.3, 14.4%)

SI.Table 2 (cont'd) Summary of estimates of CKD prevalence published between 2014 and 2022 in Europe and the US

USRDS 2019 [R22-2570]	United States	2015-2018	NHANES	9901	20+ y	Overall: 14.4% - Stage G3: 5.8% - Stage G4: 0.04% - Stage G5: 0.1%
Nichols 2020 [R20-4014]	United States	2016-2017	Retrospective study	Overall: 146 132 CKD: 21 252	Overall: 59.4 (14.3) CKD: 73.3 (11.2)	Overall: 14.5%
Saran 2021 [R22-3513]	United States	2014	Cross-sectional/ survey	7 million VA users	NR	Liberal CKD definition: 36.3% Strict CKD definition: 16.4%
Nitta 2015 [R22-3572]	Japan	2006-2015	KEEP of Japan/IKEAJ	KEEP: 1947 Non-KEEP: 747	KEEP: Mean (SD) 56.9 (16.4)	KEEP: 26.5% Non-KEEP patients: 13.8%
CK-NET 2019 [R20-3726]	China	2013-2019	HQMS CHIRA COTRS	887 816	NR	Overall: 4.8% Patients with: - Hypertension: 11.3% - Cardiovascular disease: 7.7% - Diabetes mellitus: 13.9%
Sundström 2022 [R22-3518]	11 countries	1958-2021 (Varied by country)	Health registries	2.4 million	Mean (SD) Canada: 68 (17) Germany: 77 (11) The Netherlands: 75 (12) Norway 70 (16) Spain76 (14) Sweden 68 (19) UK: 75 (14)	Possible CKD: 10.0% (8.7-11.4%)[1] Measured CKD: 7.0% (5.6-8.5%)[1] Persistent CKD: 5.6% (3.4-7.6%) Diagnosed CKD: 3.7% (2.6-4.8%)[1]

SI.Table 2 (cont'd) Summary of estimates of CKD prevalence published between 2014 and 2022 in Europe and the US

Van Rijn 2020 [R22-3568]	61 countries	2016	Global Health Data Exchange	NR	NR	High income countries: Median 6.3% (Range: 5.5-10.4%) Central/Eastern Europe: Median 8.7% (Range: 7.6-13.7% Other regions: Median 10.7% (Range:7.4-13.1%) 10.7%

Liberal definition: Presence of ≥1 at any time between FY2006 and FY2014: ICD-9-CM CKD-related diagnosis, ≥1 eGFR <60 mL/min/1.73 m^2, or ≥1 proteinuria measurement (including urine dipstick alone) categorised as moderate or severe. Strict definition: Consistent with the KDIGO definition, based on the presence of any of the following: ICD-9-CM CKD-related diagnosis, persistent eGFR <60 mL/min/1.73 m^2 (≥2 values at least 90 days apart), or with the most recent quantitative assessment of albuminuria or proteinuria (i.e. not including dipstick) being moderate or severe.

[1]Possible CKD, patients with a CKD diagnosis or one pathological uACR or eGFR measurement; Measured CKD, patients with KDICGO confirmed CKD using uACR and eGFR; Diagnosed CKD, patients with a registered CKD diagnosis.

Based on the Global Burden of Diseases, Injuries, and Risk Factors Study, there were 697.5 million (95% CI 649.2, 752.1) cases of CKD in 2017 worldwide, resulting in an age-standardised prevalence of 8724 per 100 000 population (95% CI 8124, 9403), with an increase of 1.2% (95% CI -1.1, 3.5) from 1990 to 2017 [R22-0692]. Age-standardised prevalence estimates originating from Europe varied extensively for the year 2017, ranging from 5034 per 100 000 population (95% CI 4647, 5468) in Spain to 12 832 per 100 000 population (95% CI 11 918, 13 878) in Russia. In the US, the age-standardised prevalence rate of CKD for 2017 was estimated at 8144 per 100 000 population (95% CI 7615-, 783). Global and country-specific prevalence estimates for the year 2017, along with the percentage change in prevalence between 1990 and 2017, are summarised in SI.Table 3.

SI.Table 3 Age-standardised prevalence of CKD in 2017 and percentage change by location between 1990 and 2017

Location	Age-standardised rate per 100 000 in 2017 (95% CI)	Percentage change in age-standardised rates between 1990 and 2017
Global	8724 (8124 to 9403)	1.2% (-1.1 to 3.5)
Central Europe	7659 (7115 to 8282)	-2.7% (-6.2 to 1.4)
Albania	7259 (6756 to 7864)	-1.1% (-5.2 to 3.1)
Bosnia and Herzegovina	8273 (7655 to 8943)	5.9% (1.3 to 10.4)
Bulgaria	8000 (7420 to 8630)	2.6% (-0.7 to 5.9)
Croatia	7779 (7206 to 8390)	1.2% (-3.1 to 6.2)
Czech Republic	7998 (7442 to 8628)	-2.5% (-7.0 to 2.8)
Hungary	8204 (7596 to 8881)	1.0% (-2.4 to 4.5)
Montenegro	8118 (7528 to 8773)	-1.5% (-5.0 to 2.4)
North Macedonia	8308 (7720 to 8982)	2.4% (-1.7 to 6.9)
Poland	7271 (6702 to 7943)	-6.0% (-12.9 to 0.9)
Romania	7292 (6716 to 7930)	-4.9% (-7.9 to -1.9)
Serbia	8421 (7846 to 9069)	-0.5% (-4.1 to 3.3)
Slovakia	7736 (7188 to 8341)	-3.1% (-7.2 to 1.3)
Slovenia	7581 (7056 to 8179)	-1.1% (-5.7 to 3.2)
Eastern Europe	12 408 (11 509 to 13 389)	3.0% (0.1 to 6.5)
Belarus	11 089 (10 287 to 12 028)	-1.6% (-6.6 to 4.7)
Estonia	12 058 (11 180 to 13 022)	3.6% (0.7 to 6.5)
Latvia	11 899 (11 041 to 12 884)	5.3% (0.8 to 9.6)
Lithuania	11 328 (10 507 to 12 282)	1.1% (-2.9 to 5.7)
Moldova	11 355 (10 494 to 12 260)	1.2% (-2.1 to 5.4)

SI.Table 3 (cont'd) Age-standardised prevalence of CKD in 2017 and percentage change by location between 1990 and 2017

Location	Age-standardised rate per 100 000 in 2017 (95% CI)	Percentage change in age-standardised rates between 1990 and 2017
Russia	12 832 (11 918 to 13 878)	4.5% (1.4 to 8.1)
Ukraine	11 571 (10 707 to 12 495)	-1.6% (-4.8 to 2.1)
Western Europe	5446 (5069 to 5894)	-5.0% (-7.4 to -2.6)
Andorra	5243 (4883 to 5674)	0.8% (-3.7 to 5.5)
Austria	5557 (5173 to 6011)	5.3% (1.7 to 9.0)
Belgium	5642 (5238 to 6088)	-1.4% (-4.9 to 1.9)
Cyprus	6108 (5693 to 6585)	-6.4% (-9.6 to -3.0)
Denmark	5816 (5400 to 6285)	4.9% (1.8 to 8.1)
Finland	5761 (5354 to 6220)	-4.5% (-8.6 to -0.2)
France	5242 (4858 to 5697)	-1.7% (-6.0 to 2.5)
Germany	5687 (5256 to 6173)	-4.7% (-7.7 to -1.4)
Greece	5342 (4962 to 5806)	-5.3% (-9.1 to -1.1)
Iceland	5235 (4848 to 5703)	0.4% (-4.8 to 6.0)
Ireland	5985 (5552 to 6485)	-4.0% (-8.4 to 0.7)
Israel	6246 (5810 to 6757)	0.6% (-2.1 to 3.3)
Italy	5156 (4792 to 5602)	-9.2% (-12.8 to -6.1)
Luxembourg	6011 (5558 to 6548)	-3.3% (-7.3 to 0.7)
Malta	6053 (5622 to 6550)	-5.3% (-8.6 to -1.7)
Norway	5767 (5363 to 6220)	10.1% (7.2 to 12.8)
Portugal	5817 (5416 to 6289)	-3.8% (-8.4 to 0.8)
Spain	5034 (4647 to 5468)	-5.9% (-10.3 to -1.6)
Sweden	6839 (6362 to 7400)	3.0% (0.3 to 5.7)
Switzerland	5734 (5321 to 6199)	-1.2% (-5.7 to 3.5)
The Netherlands	6142 (5688 to 6653)	1.3% (-3.1 to 6.1)
United Kingdom	5167 (4819 to 5589)	-11.4% (-13.7 to -8.9)
North America	7919 (7403 to 8540)	0.2% (-3.5 to 3.9)
United States	8144 (7615 to 8783)	0.1% (-3.6 to 3.8)

Data source: GBD Chronic Kidney Disease Collaboration [R22-0692].

Several identified studies also reported prevalence of CKD by disease stage/risk. As presented in the heat map featured in SI.Figure 1, the distribution of NHANES participants in

the US aged ≥20 years according to the KDIGO 2012 risk categories (based on eGFR and uACR [R13-4387], was as follows: 10.5% moderate risk, 2.6% high risk, and 1.3% very high risk. A similar distribution, based on KDIGO 2012 risk categories, was found in a study conducted in the general population of Italy, that was included in a recent systematic review published at the end of 2021: 11.5% moderate risk, 3.6% high risk, and 0.4% very high risk [R22-2981]. Based on the French CKD-REIN cohort study, which is a national prospective cohort study conducted across 40 health care facilities with outpatient nephrology care, the distribution of patients according to the risk of CKD progression was as follows: 6.5% moderate risk, 15.9% high risk and 65.5% very high risk [R22-3452]. In the international CaReMe study, the majority (42%) of individuals with measured CKD were in KDIGO eGFR stage 3A (moderate risk), while 20% were stage 3B (high risk), and 9% were classified as stage G4 or higher (very high risk); these proportions were consistent across countries [R22-3518]. Results from a Canadian registry reported rates of CKD by stage as 3a (31.8 per 1000), followed by stage 3b (25.3 per 1000), stage 4 (11.7 per 1000), and stage 5 (3.3 per 1000) [R22-3571].

SI.Figure 1 Distribution of US adults (≥20 years) according to KDIGO CKD risk categories: NHANES 2015-2018

Prognosis of CKD by eGFR and Albuminuria Categories: KDIGO 2012				**Persistent albuminuria categories Description and ranges**			**Total**
				A1	**A2**	**A3**	
				Normal to mildly increased	**Moderately increased**	**Severely increased**	
				<30 mg/g <3 mg/mmol	**30-300 mg/g 3-300 mg/mmol**	**>300 mg/g >30 mg/mmol**	
eGFR categories (mL/min/1.73 m2) Description and range	**G1**	**Normal or high**	**≥90**	57.7%	4.3%	0.64%	62.6%
	G2	**Mildly decreased**	**60-89**	27.9%	2.7%	0.38%	31.0%
	G3a	**Mildly to moderately decreased**	**45-59**	3.4%	0.73%	0.25%	4.4%
	G3b	**Moderately to severely decreased**	**30-44**	0.89%	0.40%	0.15%	1.4%
	G4	**Severely decreased**	**15-29**	0.10%	0.09%	0.19%	0.39%
	G5	**Kidney failure**	**<15**	0.01%	0.02%	0.09%	0.12%
Total				90.0%	8.3%	1.7%	100%

Participants aged ≥20 years with serum creatinine and uACR measurements.

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

Data source: NHANES [R13-4387].

SI.1.3 Demographics of the population in the proposed indication – age, sex, racial and/or ethnic origin and risk factors for the disease

The demographic characteristics of adults with CKD in terms of the distribution of age, sex, and race/ethnicity are consistent across studies and regions. Most adults with CKD are older, White, and female. According to the US NHANES conducted over 4 distinct 4-year periods (2003-2006, 2007-2010, 2011-2014, and 2015-2018), more than half of adults (≥20 years) with CKD were female and non-Hispanic White, respectively, ranging from 57.2% to 59.7% and from 57.0% to 64.7% across survey years [R22-3198]. The mean age of adults with CKD was consistent across the survey years ranging from 60-61 years. A summary of key characteristics of the adults with CKD reported from NHANES is found in SI.Table 4.

SI.Table 4 Age-standardised characteristics by survey years and CKD status in adults (≥ 20 years) in the US: NHANES 2003-2018

Characteristics	Total sample (N=39 569)	Participants with CKD (%)					
		Total (n=7161)	2003-2006 (n=1635)	2007-2010 (n=1926)	2011-2014 (n=1786)	2015-2018 (n=1814)	p-value[a]
Age, Mean (SD), years	47 (16.8)	61 (17.3)	61 (17.8)	61 (18.6)	60 (17.1)	61 (16.0)	0.45
Female	51.6	58.2	57.7	58.3	59.7	57.2	0.78
Race/Ethnicity							
NH Whites	67.4	60.8	61.5	64.7	60.8	57.0	
NH Blacks	10.8	13.9	14.1	12.9	14.2	14.1	0.55
Hispanics	14.2	17.1	15.9	17.1	17.3	17.8	
Other	7.5	8.2	8.5	5.3	7.6	11.2	
Education level							
Below high school	16.2	21.0	21.9	24.5	21.2	17.4	
High School	55.1	57.9	61.4	54.7	55.7	59.8	0.1
College/Above	28.7	21.0	16.7	20.9	23.1	22.7	
Family income							
Low	22.5	29.9	26.3	29.1	35.8	27.3	
Middle	31.1	33.7	34.8	31.9	31.3	37.0	0.048
High	46.4	36.4	38.9	39.0	32.9	35.8	
Hypertension 2017 ACC/AHA	44.9	59.6	58.3	59.0	59.7	61.4	0.66
Hypertension JNC7	30.5	47.0	47.8	45.9	45.4	49.1	0.36
Diabetes	11.2	24.8	23.2	23.9	23.9	27.7	0.18

SI.Table 4 (cont'd) Age-standardised characteristics by survey years and CKD status in adults (≥ 20 years) in the US: NHANES 2003-2018

Characteristics	Total sample (N=39 569)	Participants with CKD (%)					
		Total (n=7161)	2003-2006 (n=1635)	2007-2010 (n=1926)	2011-2014 (n=1786)	2015-2018 (n=1814)	p-value[a]
High cholesterol	38.3	43.2	43.2	40.3	45.9	42.6	0.58
High triglyceride	35.7	43.5	39.6	45.0	43.2	45.9	0.26
Low HDL	29.5	36.3	32.0	40.8	36.3	36.4	0.07
Obesity	36.5	46.4	42.9	43.7	44.7	53.5	0.029
Abdominal obesity	55.6	64.4	63.8	61.5	63.7	68.4	0.2
Metabolic syndrome	33.6	47.5	45.4	47.0	47.2	54.5	0.2
Insufficient aerobic PA	34.4	43.0	-	46.2	44.2	39.1	0.11
Current tobacco smoker	21.2	22.0	23.7	24.1	21.9	19.0	0.21

[a]p-values were obtained by analysis of variance (for continuous variables) or chi-square tests (for categorical variables).

Notes: Hypertension was defined as a SBP/DBP ≥130/ 80 mmHg or self-report of any taking antihypertensive drugs; Hypertension was defined as a SBP/DBP ≥140/90 mmHg or self-report of taking any antihypertensive drugs; The high total cholesterol level was defined as ≥240 mg/dl total cholesterol level; High serum triglycerides was defined as ≥150 mg/dL; Low HDL concentration was defined as <40 mg/dL for men and <50 mg/dL for women; Any person reported taking antilipid drugs was also defined as having high total cholesterol, high serum triglycerides, or low HDL; Obesity was defined as body mass index ≥30 kg/m^2; Abdominal obesity was defined as ≥102 cm for men and ≥88 cm for women; Metabolic syndrome was defined as having at least 3 of the 5 following conditions: abdominal obesity (defined above); high serum triglycerides (defined above); low HDL concentration (defined above); raised SBP/DBP (i.e. ≥135/85 mmHg); and raised fasting glucose level (i.e. ≥100 mg/dL); People who reported that they were taking antihypertensive, antilipid, and antidiabetic drugs were also defined as having raised BP, high triglyceride/low HDL, and raised blood glucose, respectively; Diabetes was defined as the glycohemoglobin of ≥6.5%, previous diagnosis by a doctor of having diabetes, or taking of any antidiabetic drugs; Insufficient aerobic PA was defined as <150 min of moderate, vigorous, or transportation activity in a regular week; The PA data was available from 2007 to 08 survey year.

Data source: [R22-3198]

Similar demographic characteristics were reported in the USRDS ADR that included 181 090 patients with CKD from the Medicare FFS, 701,351 from the MA, and 73 052 from the commercially insured population in 2019 [R22-2570]. As summarised in SI.Table 5, regardless of insurance type, the demographic characteristics of beneficiaries with CKD differed from those without. Individuals with CKD were older, were more frequently male (FFS: 47.7% versus 43.3%; MA: 45.3% versus 41.2%; commercial insurance, 56.8% versus 51.2%), and of Black race (FFS: 9.6% versus 6.4%; MA: 11.2% versus 7.7%; commercial insurance, 11.1% versus 7.9%).

SI.Table 5 Demographic characteristics of insured adults in 2019 in the US

Characteristics	Participants (%)					
	Medicare FFS		Medicare Advantage		Commercial	
	No CKD	CKD	No CKD	CKD	No CKD	CKD
	(N=1 094 477)	(N=181 090)	(N=3 797 724)	(N=701 351)	(N=6 496 606)	(N=73 052)
Age (in years)						
18-39	-	-	-	-	45.6	13.8
40-54	-	-	-	-	33.2	33.1
55-65	-	-	-	-	21.1	53.1
66-69	26.6	13.5	24.7	13.2	-	-
70-74	29.3	21.4	30.1	22.4	-	-
75-79	19.5	21.4	21.2	22.6	-	-
80-84	12.4	18.7	12.5	18.6	-	-
85+	12.2	25.1	11.5	23.1	-	-
Sex						
Female	56.7	52.3	58.8	54.7	48.8	43.2
Male	43.3	47.7	41.2	45.3	51.2	56.8
Race/Ethnicity						
White	85.6	83.4	56.1	55	57.1	59.3
Black	6.4	9.6	7.7	11.2	7.9	11.1
Hispanic	1.5	1.5	8.7	11.6	12.2	11.7
Asian	2	2.1	3.2	2.9	5.3	4
Native American	0.5	0.5	-	-	-	-
Other	1.7	1.7	-	-	-	-
Unknown	2.3	1.3	24.4	19.4	17.2	13.9

Data sources: Medicare 5% sample (Medicare FFS) and Optum de-identified Clinformatics Data Mart Database (Medicare Advantage and Commercial). 31 Dec 2019 point prevalent enrollees aged ≥66 years (Medicare) or 18-65 years (Commercial). [R22-2570]

SI.1.4 Risk factors

Factors that increase risk for CKD in adults [R22-3404, R22-3448, R22-3412, R22-3417, R22-3418, R22-3443, R22-3444, R22-3458, R22-3460, R22-3421, R22-3449, R22-3451, R22-3453, R22-3464, R22-3431, R22-3467, R22-3469, R22-3470, R22-3471]:

- Socio-demographic characteristics:
  - Female gender
  - Older age
  - Race/ethnicity
    - African American (compared to White)
    - Non-Hispanic Black (compared to non-Hispanic White)
    - Other races than Caucasian
  - Lower SES (compared to higher)
  - Lower education level (compared to higher)
  - Lower levels of income (compared to higher)
- History of CVD
  - Chronic HF
  - CHD
  - History of myocardial infarction
  - Hypertension (prior history and current)
- Endocrine and metabolic
  - DM
  - Duration of DM ≥10 years (compared to <10 years)
  - Dyslipidaemia
  - Metabolic syndrome
  - Obesity
    - Morbidly obese (BMI ≥35 kg/m^2) compared to normal weight persons
    - Obese compared to non-obese
- HCV infection (current)
- Hyperuricemia
- History of nephrolithiasis
- NAFLD (current)
- Psoriasis (current)

- Worse lowest nocturnal oxygen saturation (current)
- Lifestyle factors
    - High salt intake
    - Unhealthy Western-type dietary pattern (i.e. high intakes of all kinds of red and/or processed meats, refined grains, sweets, high-fat dairy products and high-fat gravy) (compared to healthy pattern)
    - Pesticide use (highest category of use compared to non-users)
        - Atrazine, metolachlor, alachlor, paraquat and pendimethalin
        - More than one doctor visit due to pesticide use
        - Hospitalisation due to pesticide use
    - Smoking (compared to never smoked)
        - >20 cigarettes a day
        - Current and former smokers
        - Ever-smokers, current smokers and former smokers
    - Physical inactivity
        - Moderately active compared to very active
        - Sedentary compared to physically active

Factors that decrease risk for CKD in adults [R22-3418, R22-3443, R22-3400, R22-3411, R22-3419, R22-3468]:

- Lifestyle factors
    - Alcohol consumption
        - Low or moderate consumption (compared to no consumption)
        - Light, moderate, or heavy alcohol intake (compared to minimal alcohol intake)
    - Diet
        - Higher healthy dietary pattern (compared to unhealthy category)
        - Higher diet quality (compared to lower)
        - Higher dietary potassium intake (compared to lower)
        - Higher vegetable intake (compared to lower)

SI.1.5 The main existing treatment options

SI.1.5.1 Summary of evidence and key insights

Current treatment in clinical practice

- Adequate control of hypertension and inhibiting the renin-angiotensin system, using either ACEis or ARBs, are the basis for the management of patients with CKD. These agents reduce glomerular hyperfiltration and albuminuria and slow the decline in kidney function [R14-0002, R22-3414, R22-3452, R22-3447, R22-3469, R22-3402, R22-3403, R22-3407, R22-3408, R22-3416, R22-3446, P14-05085]. However, renin angiotensin system inhibitors may be associated with important risks, such as an increase in serum potassium levels, which can restrict their use [R08-0910].
- Diuretics and other antihypertensive agents are often required, in addition to ACEis and ARBs, to optimise hypertension control and mitigate disease progression; diuretics may also help control serum potassium levels [R22-3452, R22-3447, R22-3403]
- Statins [R14-0002, R22-3452, R22-3403, P14-05085]
- Anaemia is known to increase the risk of hospitalisation, cognitive and functional impairment, and CVD, especially left ventricular hypertrophy. Treatment of CKD-associated anaemia is based on erythropoietin and iron supplementation, many patients require parenteral iron therapy, since intestinal iron absorption is reduced in CKD [R22-3452, P14-05085].
- Uric acid [R22-3452, P14-05085]
- Parathyroid hormone [R22-3452, P14-05085]
- Vitamin D and calcitriol are used in patients with low calcium blood levels [R22-3452, P14-05085]
- Diet is important to control hypertension and prevent volume overload. Low-protein diet, with sodium and potassium restriction, is recommended to prevent electrolyte imbalances. Hyperphosphatemia may be controlled with judicious restriction of dietary phosphorus and the use of postprandial phosphate binders, either calcium-based salts (calcium carbonate or acetate) or non-absorbed agents (e.g. sevelamer) [R22-3452, R22-3469, P14-05085, R22-3198].
- Dialysis is the main treatment for patients with ESRD. Dialytic options include HD and PD [P22-07789, R22-3399, R22-3415].

SI.1.6 Natural history of the indicated condition in the population, including mortality and morbidity

SI.1.6.1 Stages of CKD

The epidemiology of the natural course of CKD is well described in the literature. The KDIGO classification of CKD is a widely used classification system, which includes stages based on GFR and albuminuria category [R13-4387].

KDIGO GFR categories for CKD stages are defined as follows:

- G1 (Normal or high): ≥90 mL/min/1.73 m^2
- G2 (Mildly decreased): 60-89 mL/min/1.73 m^2
- G3[a] (Mildly to moderately decreased): 45-59 mL/min/1.73 m^2
- G3[b] (Moderately to severely decreased): 30-44 mL/min/1.73 m^2
- G4 (Severely decreased): 15-29 mL/min/1.73 m^2
- G5 (Kidney failure): <15 mL/min/1.73 m^2

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfil the criteria for CKD.

KDIGO albuminuria categories for CKD stages are defined as follows:

- A1 (Normal to mildly increased): AER <30 mg/24 or ACR <3 mg/mmol or ACR <30 mg/g
- A2 (Moderately increased[a]): AER 30-300 mg/24 or ACR 3-30 mg/mmol or ACR <30-300 mg/g
- A3 (Severely increased[b]): AER >300 mg/24 or ACR >30 mg/mmol or ACR >300 mg/g

[a]Relative to young adult level
[b]Including nephrotic syndrome (albumin excretion usually 42200 mg/24 hours [ACR 42220 mg/g; 4220 mg/mmol]).

SI.1.6.2 Mortality

Based on the GBD, there were 1.2 million (95% CI 1.2, 1.3) deaths due to CKD worldwide in 2017, ranking CKD as the twelfth leading cause of death [R22-0692]. Globally in 2017, the age-standardised mortality rate from CKD was estimated at 15.9 per 100 000 population (95% CI 15.5, 16.3), with an increase of 2.8% (95% CI -1.5, 6.3) since 1990. Age-standardised mortality rates from Europe in 2017 varied extensively across countries, ranging from 3.1 per 100 000 population (95% CI 2.9, 3.3) in Belarus to 14.8 per 100 000 population (95% CI 12.4, 16.1) in Serbia. In the US, the age-standardised mortality rate from CKD in 2017 was estimated at 14.6 per 100 000 population (95% CI 14.3, 14.9).

In 2012, KDIGO reported on the risk of all-cause mortality in general population cohorts of patients with uACR based on estimates from a meta-analysis that expressed eGFR and albuminuria as categorical variables [R13-4387]. In the heat map presented , the RR for all-cause mortality is statistically higher for eGFR <60 mL/min/1.73 m^2, regardless of the level of albuminuria. Furthermore, higher albuminuria categories were associated with a higher mortality rate for all eGFR categories. Similar results were reported for cardiovascular mortality.

In a retrospective cohort study based on the Kaiser Permanente Renal Registry, a total of 1 120 295 adult outpatients with at least one measurement of serum creatinine were identified over the period 1996-2000 [R10-5394]. In this study, the risk of all-cause mortality increased as the eGFR level decreased when compared to eGFR ≥60 mL/min/1.73 m^2 (eGFR of 45-59 mL/min/1.73 m^2: aHR=1.2 [95% CI 1.1, 1.2]; eGFR of 30-44 mL/min/1.73 m^2: aHR=1.8 [95% CI 1.7, 1.9]; eGFR of 15-29 mL/min/1.73 m^2: aHR=3.2 [95% CI 3.1, 3.4]; and eGFR <15 mL/min/1.73 m^2: aHR=5.9 [95% CI 5.4, 6.5]). The aHR of cardiovascular events and hospitalisation also increased as levels of eGFR decreased.

According to the USRDS ADR, the standardised all-cause mortality rate among Medicare FFS beneficiaries aged ≥66 years with CKD declined by 22.3% over a decade, from 121.5 per 1000 PY in 2009 to 94.4 per 1000 PY in 2019 [R22-2570]. Estimates according to age, sex, and race/ethnicity, similar mortality rates were similar, as summarised in SI.Table 7.

SI.Figure 2 Summary of meta-analysis (pooled relative risks) for all-cause mortality in general population cohorts defined according to categories of eGFR and albumin-to-creatinine ratio

	ACR <10	**ACR 10-29**	**ACR 30-299**	**ACR ≥300**
eGFR >105	1.1	**1.5**	**2.2**	**5.0**
eGFR 90-105	Reference	**1.4**	**1.5**	**3.1**
eGFR 75-89	1.0	**1.3**	**1.7**	**2.3**
eGFR 60-74	1.0	**1.4**	**1.8**	**2.7**
eGFR 45-59	**1.3**	**1.7**	**2.2**	**3.6**
eGFR 30-44	**1.9**	**2.3**	**3.3**	**4.9**
eGFR 15-29	**5.3**	**3.6**	**4.7**	**6.6**

Notes: All results are adjusted for covariates and compared to the reference cell. Each cell represents a pooled RR from a meta-analysis; bold numbers indicate statistical significance at $p<0.05$. Incidence rates per 1000 PY for the reference cells are 7.0 for all-cause mortality. Colours reflect the ranking of adjusted RR. The point estimates for each cell were ranked from 1 to 28 (the lowest RR having rank number 1, and the highest number 28). The categories with a rank number 1-8 are green, rank numbers 9-14 are yellow, the rank numbers 15-21 are orange, and the rank numbers 22-28 are coloured red.
Data source: KDIGO 2012 Clinical practice guideline for the evaluation and management of CKD [R13-4387].

SI.Table 6 Standardised all-cause mortality of CKD in older adults stratified by age, sex, and race/ethnicity in the US

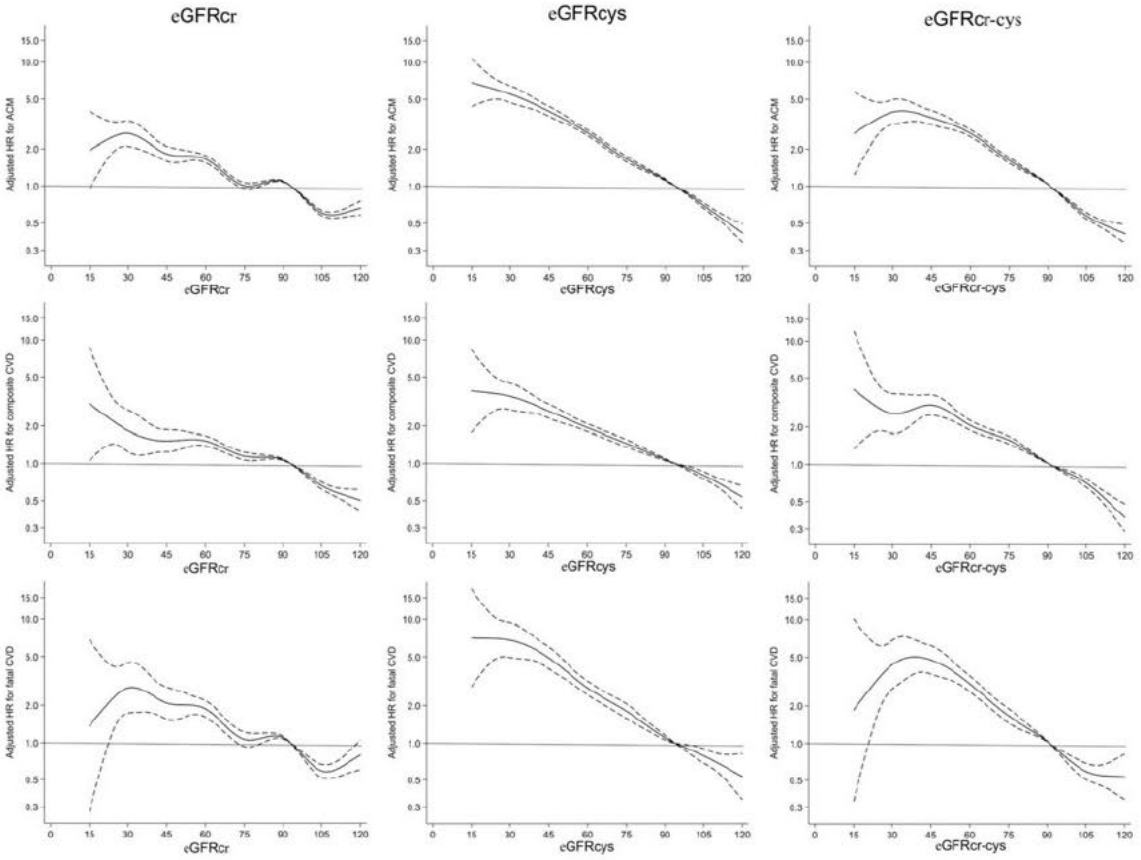
	Standardised all-cause mortality per 1000 PY										
	2009	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Overall	121.5	120.2	114	115.1	112.3	106.9	106.9	103.5	99.3	97.7	94.4
Age (years)											
66-69	66.5	68.6	60.7	65.1	64.2	57.1	59.6	61.4	56.6	54.3	50.7
70-74	81.5	81	78.3	74	71.7	72.1	66.5	68.1	60.2	60.9	60.3
75-84	130.6	126.4	118.5	120.9	117.8	112.3	110.1	104.1	102.1	98.7	93.7
85+	266.5	263.3	259.8	261.6	253.7	242.7	251.6	235.9	235.6	234.1	230.1
Sex											
Male	134.3	132.6	125.9	128.1	122.7	117.7	117.3	115.2	108.3	108.9	104.5
Female	112.5	111.6	106.1	106.1	105.1	99.6	99.8	95.2	93.2	89.7	87.3
Race/Ethnicity											
White	122.7	121.6	115.7	116.9	113.8	109	108.4	105.1	100.8	98.8	95.3
Black	123.6	118.6	112.9	115.9	112.1	105.8	108.1	104.9	98.7	99.2	96.1

Note: Data in this table have been standardised by age, sex, and race/ethnicity.

Data source: Medicare 5% random sample database [R22-2570]. 01 January point prevalent Medicare FFS beneficiaries aged ≥66 years.

Using data from the UK Biobank, a total of 440 526 participants were identified across 22 assessment centres [R22-3445]. In this study, eGFR was calculated using the CKD-EPI formula using serum creatinine (eGFRcr), cystatin C (eGFRcys) and creatinine-cystatin C (eGFRcr-cys). As presented in SI.Figure 3, eGFRcys measure was strongly associated with all-cause mortality, composite fatal/non-fatal CVD and fatal CVD outcomes, whereas traditional creatinine-based eGFR measures were weakly associated with these outcomes. Similar findings were reported in a meta-analysis conducted between March 2011 and June 2012, which assessed the associations between kidney disease measures and mortality as well as ESRD in participants with and without diabetes [R15-5162].

SI.Figure 3 Adjusted association between eGFR measures and all-cause mortality and CVD outcomes in the UK



Note: Adjusted for age, sex, ethnicity, systolic blood pressure, diastolic blood pressure, antihypertensive medications, smoking, diabetes, statin use, total and HDL cholesterol.

Data source: [R22-3445]. Reproduced without permission.

SI.1.6.3 Morbidity (natural history)

According to the USRDS ADR, regardless of CKD status, the standardised all-cause hospitalisation rates were higher in the population aged ≥ 66 years than in younger individuals [R22-2570]. Among this older adult population, higher estimates of hospitalisation were reported in males; however, the relative difference in hospitalisation between males and females was less marked in individuals with CKD than in those without CKD. Similarly, regardless of CKD status, standardised all-cause hospitalisation rates were higher in Black individuals than in White individuals. In commercially insured younger adults aged 18-64 years, the standardised rate of all-cause hospitalisation among those with CKD (any stage) was over four times higher compared to individuals without CKD (36.3 per 1000 PY versus 148.5 per 1000 PY). More specifically, the standardised hospitalisation rate in patients with stage 4-5 CKD was more than double that of patients with stage 3 CKD, and about 12 times that of individuals without CKD. A summary of standardised all-cause hospitalisation rates stratified by age, sex, and race/ethnicity can be found in SI.Table 7.

SI.Table 7 Standardised all-cause hospitalisation rate in the US, by demographics, 2019

	Standardised all-cause hospitalisation per 1000 PY			
	No CKD	**All CKD**	**CKD Stage 3**	**CKD Stages 4-5**
Older Adults[1]				
Age (years)				
66–69	144.7	476.6	490.9	876.6
70–74	175.9	500.7	503.5	855.2
75–84	255.7	576.5	564.8	913
85+	417.9	723.1	701.6	928.5
Sex				
Female	221.6	544.3	542	892.3
Male	236.9	559.5	556.2	890.7
Race/Ethnicity				
White	231	550.6	548.3	884.4
Black/African American	248.8	633.1	612	972.2
Hispanic	198	562.2	560.7	820
Other	167.1	437.9	453.2	862.2
Young Adults[2]				
18-64 years	36.3	148.5	201.4	413.6

Note: Data in this table have been standardised by age, sex, and race/ethnicity.

Data sources:

[1]Medicare 5% random sample database

[2]Optum de-identified Clinformatics Data Mart database (for commercial insurance cohorts) database [R22-2570]. 01 Jan 2019 point prevalent enrollees, Medicare FFS beneficiaries aged ≥66 years and Optum beneficiaries aged 18-64 years.

SI.Table 8 Standardised rate of hospitalisation in older adults stratified by CKD status and CKD stage in 2019, in the US

Cause of Hospitalisation	Standardised hospitalisation per 1000 PY			
	No CKD	All CKD	Stage 3	Stages 4-5
CVD	55.3	147.2	151.0	276.4
Infection	50.0	132.7	128.5	199.0
Diabetes	1.8	10.3	10.5	18.9
Cancer	9.5	14.9	14.5	16.4
GI bleeding	5.0	12.7	12.7	21.8
Non-infectious lung disease	9.3	22.7	22.5	26.2
Fracture	13.3	20.0	20.0	23.9
Other diseases	87.1	189.9	187.1	296.7

Note: Data in this table have been standardised by age, sex, and race/ethnicity.
Data source: Medicare 5% random sample database [R22-2570]. 1 Jan 2019 point prevalent Medicare FFS beneficiaries aged ≥66 years.

SI.1.7 Important comorbidities

In a cross-sectional analysis of a primary care dataset covering 1 274 374 adults in Scotland in 2007, patients with CKD had a higher mean number of comorbidities than people without CKD (3.8 [SD 2.2]) versus 1.2 [SD 1.6], respectively) (see SI.Table 2) [R22-3459]. After standardising by age, sex, and socioeconomic status, patients with CKD were considerably more likely to have 1 condition (OR 6.5 [95% CI 6.0, 7.1]), 2-3 conditions (OR 15.2 [95% CI 14.0, 16.5]), 4- 6 conditions (OR 26.6 [95% CI 24.4, 28.9]), and ≥7 conditions (OR 41.9 [95% CI 38.3, 45.8]).

Below is a list (non-exhaustive) of important comorbidities experienced by individuals with CKD [R22-3448, R22-2570, R22-3445, R22-3447, R22-3444, R22-3399, R22-3422, R22-3405, R22-3459, R22-3465, R22-3466]:

- Anaemia
- Asthma
- Blindness or low vision
- Bronchiectasis
- Cancer
- Cerebrovascular disease
- Chronic liver disease
- COPD
- Chronic sinusitis

- CVD
  - AMI
  - ASCVD
  - AF
  - CVA/TIA
  - CHD
  - CHF
  - CAD
  - HF (known risk factor)
  - Hypertension (known risk factor)
  - Ischaemic heart disease
  - PAD
  - Valvular heart disease
- Diabetes
- Diverticular disease of intestine
- Dyslipidaemia (known risk factor)
- Dyspepsia
- Glaucoma
- Gout
- Hyperuricemia
- Infections
  - HCV
  - HBV
  - HIV
  - SARS-CoV-2
  - UTIs
- Irritable bowel disease
- Liver disease (known risk factor)
- Malnutrition
- Mental health conditions
  - Alcohol abuse
  - Anorexia or bulimia

  - Anxiety and associated conditions
  - Dementia
  - Depression
  - Learning disability
  - Schizophrenia or bipolar affective disorder
  - Other psychoactive substance misuse
- Migraine
- MS
- Neuropathy
- Obesity (known risk factor)
- Parkinson's disease
- Prostate disorders
- Psoriasis or eczema
- Respiratory condition
- Retinopathy
- Thyroid disorder

SI.2 HEART FAILURE

SI.2.1 Incidence

The incidence of HF has been investigated in several prospective or retrospective cohort studies in Europe and North America but remains poorly documented in Asia-Pacific. A summary of studies published from 1970 to 2021 is presented in the table below.

The incidence estimates of HF were higher in elderly, in men, and in certain ethnic groups such as in American Blacks than in their counterparts (SI.Table 9 and SI.Table 10). In the MESA study when the baseline comorbidities of hypertension and diabetes were adjusted, the observed differences in HF incidence between Black and White disappeared [R14-1824].

In several longitudinal US community-based samples (age ≥60 years and free of HF at baseline) from 1990 to 2009, it was observed that the overall incidence of HF was relatively stable but the incidence of HFpEF increased while HFrEF decreased during the 2 decades (SI.Table 10) [R21-2697]. In Olmsted County study, from 2000 to 2010, the age-and sex-adjusted HF incidence declined for both HF sub-types, but was greater for HFrEF than for HFpEF (p for interaction 0.08) [R19-0448].

SI.Table 9 Available data on incidence rates of HF reported between 1970 and 2021

Country	Time	Data source	Sample size, n	Age, years	Incidence per 1000 PY			Reference
					Male	Female	Total	
US	1970-1974	Kaiser Permanente Northwest Region health plan (EMR)	9272	≥65	11.7	8.6	Age-and sex-adjusted rates	[R21-2613]
	1990-1994		31399	≥65	12.7	11.8		
	1985-2006 (20-years follow-up)	Coronary Artery Risk Development in Young Adults (CARDIA)	5115	18-30 baseline; HF diagnosis before 50	0.09 0	0.11 0.008	Black White	[R21-2614]
	1994-2003	A retrospective cohort study of Medicare beneficiaries	622 789	≥65	Year 1994: 36.8 Year 2003: 32.9	Year 1994: 29.2 Year 2003: 26.4	Year 1994: 32.2 Year 2003: 29.1	[R19-4006]
	1987-2002	The ARIC cohort study	14 994	Mean age 57	-	-	5.7*	[R08-4693]
	2001-2004	Look AHEAD	5109	45 - 76			All: 4.42 HFpEF: 2.23 HFrEF:1.79	[R21-2686]
China	NR	Review	2010	NR	-	-	9	[R19-3972]
Germany	2001	Statutory health insurance database	3 132 337	All ages	6.45	6.65	6.55	[R19-3750]
	2004-2006	3 German statutory health insurance database	6 284 194	All ages	3.1	2.3	2.7	[R19-3749]
UK	1991-1994	GPRD	696 884	≥45	Definite: 9.0 Possible: 15.0	Definite: 10.0 Possible: 24.0	Definite: 9.3 Possible: 20.2	[R19-3745]
	NR	Reported by general practitioners	101 885	22-95	1.4	1.2	1.3	[R19-3744]
	2002-2014	CPRD	4 045 144	≥16	-	-	Year 2002: 3.58 Year 2014: 3.32	[R19-3743]
Italy	2000-2012	Hospital discharge forms with HF-related ICD-9 CM codes collected by the regional healthcare service	370 538	≥18	3.72	3.52	3.62	[R19-3973]

SI.Table 9 (cont'd) Available data on incidence rates of HF reported between 1970 and 2021

Country	Time	Data source	Sample size, n	Age, years	Incidence per 1000 PY			Reference
					Male	Female	Total	
Spain	2000-2007	Prospective population-based study in a White, low-middle class Mediterranean community	267 231	≥14	-	-	Year 2000: 2.96 Year 2007: 3.90	[R19-3746]
	2017 2018 2019	Retrospective analysis of EMR of patients ≥18 years from 2017 to 2019	1 853 412	≥18			2.70 (1.47 HFrEF) 2.74 (1.50 HFrEF) 2.78 (1.53 HFrEF)	[R21-2665]
Sweden	Cohort 1	Cohort 1: national health register of all patients with HF in secondary care (inpatient and outpatient) Cohort 2: EMR data from both primary and secondary care.		≥18				[R21-2648]
	2010		Cohort 1: 174 537		3.41	2.85	3.20	
	2011				3.43	2.85	3.21	
	2012				3.33	2.85	3.16	
	2013				3.25	2.70	3.04	
	2014				3.08	2.61	2.91	
	Cohort 2							
	2010		Cohort 2: 8702		4.50	4.19	4.34	
	2011				4.14	3.77	3.95	
	2012				3.86	3.40	3.63	
	2013				3.76	3.60	3.68	
	2014				3.53	3.12	3.33	
Serbia	2010-2012	Prospective observational study with inpatients and outpatients with AF		≥18	-	-	With T2DM: HF event 1.152 New-onset HF 0.133 HFrEF 0.035 HFmEF 0.035 HFpEF 0.104 Without T2DM: HF event 0.388 New-onset HF 0.085 HFrEF 0.008 HFmEF 0.021 HFpEF 0.066	[R21-2689]

***Age adjusted**

A prospective cohort study by Loehr et al. in the US described the incidence of HF among Caucasians and African Americans stratified by age categories and sexes (see table below) [R08-4693].

SI.Table 10 Estimated incidence of HF among Caucasians and African Americans stratified by age categories and sexes in the US

Age (years)	Incidence rate (per 1000 PY)				
	Caucasian		African Americans		Overall races
	Male	Female	Male	Female	
Overall	6.0	3.4	9.1	8.1	5.7
45–49	2.4	1.7	5.2	3.8	-
50–54	5.6	3.1	7.2	7.6	-
55–59	8.4	4.4	14.0	10.1	-
60–64	14.3	7.7	13.4	17.4	-

Data source: [R08-4693]

SI.Table 11 Incidence of HF in Framingham Heart and Cardiovascular Health Study participants from 1990–2009

	1990-1999	2000-2009	p-value
Number at risk	8762	6455	
Person-years follow-up	70 548	45 155	
Age at start of window, y	73 ± 8	74 ± 9	
Women, n (%)	5128 (59%)	3954 (61%))	
All HF*			
HF events, n	1367	1157	
Std HF incidence per 1000	19.7 (18.4, 21.0)	18.9 (17.7, 20.1)	0.37
HFrEF			
HFrEF events, n	491	353	
Std HF incidence per 1000	6.6 (5.9, 7.3)	6.2 (5.4, 6.9)	0.40
HFpEF			
HFpEF events, n	309	431	
Std HF incidence per 1000	4.7 (4.2, 5.2)	6.8 (6.1, 7.5)	<0.001

Participants were ≥60 years of age at the start of each decade. Std HF incidence = reported as n (95% CI), standardised to age- and sex-specific 2010 (ages 60–95) US population rates, per 1 year follow up.

*Some HF events had undetermined LVEF. HFrEF and HFpEF= heart failure with reduced (EF<50%) and preserved (EF≥50%) left ventricular ejection fraction.

Data source: [R21-2697]

SI.2.2 Prevalence

Researchers have defined HF as a global pandemic which since 2016 has affected approximately 63.6 million people worldwide [R19-0778]. Population-based studies suggest an overall prevalence of HF of 2% to 3%, increasing to 7% in the elderly [P20-01257]. The prevalence of HF increases with age, with a median prevalence of 11.8% in those aged 60 years and older [R20-0329]. Furthermore, HF prevalence is 9.2-fold higher in those aged ≥65 years than those aged 19 to 64 years [R20-0333]. In North America and Europe, more than 80% of patients with HF are aged ≥65 years, and <5% are aged ≤50 years [R20-0325].

The prevalence of CHF is projected to increase by 50% in the next 20 years because of an ageing population, improved survival from other CV diseases and improved survival rates for HF itself [P20-01257].

The frequency of HF has been investigated worldwide using different diagnostic procedures from a self-reported diagnosis of HF, a measurement of NT-proBNP alone to a more comprehensive clinical examinations and diagnosis. The study populations varied among reports from a large national health survey to a small community-based screening based on patients at high-risk for HF. The age distributions differed among studies too. Therefore, the prevalence summarised in the table below cannot be compared directly, and the interpretation of the figures need to take into account the background of each study.

SI.Table 12 Available data on prevalence of HF reported between 1992 and 2021

Country	Prevalence of HF		Study	Reference
	Year(s)	N (%)		
US	2015 – 2018	Total 6.0 million (2.1) Men 3.4 million (2.5) Women 2.6 million (1.7)	AHA Heart Disease and Stroke Statistics – 2021 update; age ≥20 years.	[P21-07079]
	2016	Total 6.2 million (2.2) Men 3.0 million (2.4) Women 3.2 million (2.1)	AHA Heart Disease and Stroke Statistics – 2019 update; age ≥20 years.	[P19-03569]
	2012	Total 5.7 million (2.2) Men 2.7 million (2.3) Women 3.0 million (2.2)	AHA Heart Disease and Stroke Statistics – 2016 update; age ≥20 years.	[P16-03952]
	2008	Total 5.7 million (2.4) Men 3.1 million (3.0) Women 2.6 million (2.0)	AHA Heart Disease and Stroke Statistics – 2012 update; age ≥20 years.	[P19-03569]

SI.Table 12 (cont'd) Available data on prevalence of HF reported between 1992 and 2021

Country	Prevalence of HF		Study	Reference
	Year(s)	N (%)		
Japan	2005	Left ventricular dysfunction Total 979 000 (1.6) Men 618 000 (2.2) Women 361 000 (1.1)	Projected based on the 2 studies below for the whole nation, aged 45 to ≥85 years	[R20-0158]
	2003 In Sado city	Isolated diastolic dysfunction Men NR (0.85) Women NR (0.54)	Sado Heart Failure Study of outpatients aged 45-84 years	[R20-0161]
	2003 In Niigata and Sado cities	Left ventricular systolic dysfunction Men NR (1.5) Women NR (0.6)	Niigata-Sado Heart Failure Study of outpatients aged 45-84 years	[R20-0162]
China	2001	4 000 000 (0.9) Men (0.7) Women (1.0)	Population-based survey 2001, aged 35-74 years	[R20-0452]
	2007-2009	Han total 36 (0.74) Men 23 (0.84) Women 13 (0.60) Uygur total 36 (1.85) Men 15 (1.42) Women 11 (1.02) Hasake total 45 (2.40) Men 29 (3.81) Women 16 (2.61)	Population-based survey in Xinjiang, aged ≥35 years. Age standardised rates.	[R20-0159]
	2010	4.0 million (NR)	Outline report on CV disease in China	[R20-0203]
	2012-2013	Men 19 (1.5) HFpEF Women 58 (4.63) HFpEF Total 77 (3.15) HFpEF	Population based survey in rural villages in North-eastern China, age-standard rates	[R21-2634]
Taiwan	2009 - 2018	Total 151 (18.6) HFrEF 64 (7.9) HFpEF 87 (10.7)	Retrospective tertiary hospital-based cohort from Taichung Veterans General Hospital, aged ≥65 years	[R21-2698]
Germany	2017	NR (6.0)	Retrospective claims database study, 40 years or older	[R20-0204]
	2001	123 925 (3.96)	Retrospective claims database study, all ages	[R19-3750]
	2004-2006	NR (1.7-1.9) Men (1.7-1.8) Women (1.6-1.7)	Retrospective database study, age- and sex-standardised to European standard population of all ages	[R19-3749]

SI.Table 12 (cont'd) Available data on prevalence of HF reported between 1992 and 2021

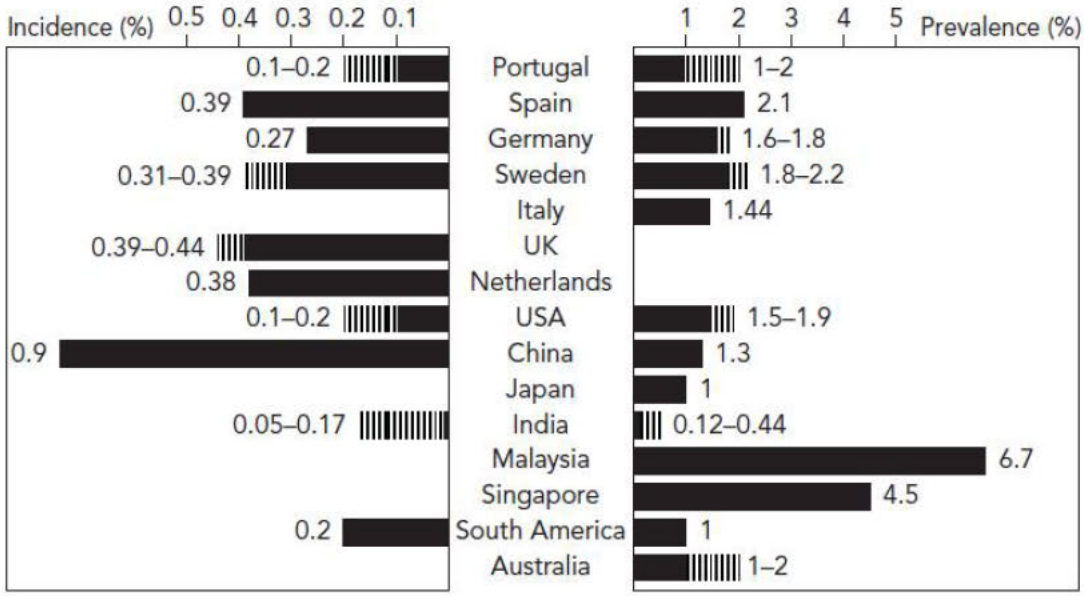
Country	Prevalence of HF		Study	Reference
	Year(s)	N (%)		
UK	2017-2018	585 614 (0.8)	Heart Failure Register, British Heart Foundation Heart and Circulatory Disease Statistics 2019	[R20-0204]
	2011	Men 94 200 (0.9) Women 105 114 (0.7)	GPRD database study 2012; standardised to the European standard population of all ages	[R20-0452]
	2006-2018	NR (0.7-0.8 England; 0.8-0.8 Scotland; 0.9-1.0 Wales, and 0.8-0.9 Northern Ireland)	QOF achievement data	[R20-0242]
	2003-2015	Total NR (1.3-2.0) Men (1.5-2.0) Women (1.0-1.2)	Wales Health Surveys: 2003/04 - 2015	[R20-0242]
	1987-2016	900 (11.1)	Genetics of Diabetes Audit and Research Tayside Scotland (GoDARTS) registry	[R21-2651]
Italy	2009	28 062 (1.4)	Retrospective database study of Italian National Health System, age ≥16 years	[R20-0208]
	2007-2010	1340 (6.7)	Population-based cross-sectional study in central Italy (PREDICTOR), aged 65-84 years	[R19-4033]
Spain	2012	88,195 (NR) 1.2% >15 years old 2.7% >44 years old	Retrospective database study in Catalonia, aged >15 years	[R20-0207]
	2000	NR (0.9)	Community-based prospective cohort study of population ≥14 years	[R19-3746]
	2007	NR (2.1)		
	2015-2017	1.86% (0.97% HFrEF)	Retrospective analysis of EMR of patients ≥18 years from 2017 to 2019	[R21-2665]
	2016-2018	1.87% (0.96% HFrEF)		
	2017-2019	1.89% (0.98% HFrEF)		
		2.09% men		
		1.17% women		
The Netherlands	2009-2010	Total 185 (30.6) Men 24.8 Women 31.0 HF previously not known 161 (27.7)	Observational study among 605 patients with T2DM aged ≥60 years	[R20-0209]
Poland	2007-2011	Total 247 (6.1) Men 141 (6.6) Women 106 (5.5) Age, gender and size of residence standardised rate was 3.0%.	PolSenior Study of a random elderly population of ≥65 years. Prevalence of NT-ProBNP >2000 pg/mL alone was reported.	[R20-0160]
	2004-2005	38 (0.69)	Community based screening of patients aged ≥55 years with either a diagnosis of HF or at least one risk factors for HF in primary care settings	[R20-0451]

SI.Table 12 (cont'd) Available data on prevalence of HF reported between 1992 and 2021

Country	Prevalence of HF		Study	Reference
	Year(s)	N (%)		
Sweden	Cohort 1	Age standardised	Age ≥18 years.	[R21-2648]
	2010	1.61	Cohort 1: national health register of all patients with HF in secondary care (inpatient and outpatient); and Cohort 2: EMR data from both primary and secondary care.	
	2011	1.66		
	2012	1.69		
	2013	1.71		
	2014	1.72		
	Cohort 2			
	2010	2.15		
	2011	2.21		
	2012	2.22		
	2013	2.23		
	2014	2.18		
Canada	2016	600 000 (NR)	Heart and Stroke Foundation of Canada 2016 report	[R20-0205]
	2006	500 000 (1.5)	--	[R19-3993]
Australia	2007 -2008	Total 277 800 (1.3) Men 100 500 (NR) Women 177 200 (NR)	CV disease Australian facts 2011 National Health Service, all ages	[R20-0238]
	2004 -2005	Total 26 300 (1.3)	National Health Service, all ages	[R20-0238]
Serbia	2010 -2012	Total 424 (23.5) New-Onset 84 (6.5)	Prospective observational study with inpatients and outpatients with AF	[R21-2689]
South Korea	2002	Total 370 000 (0.75) Men NR (0.54) Women NR (0.96)	Retrospective claims database study National Health Information Database	[R20-0202]
	2013	Total 755 000 (1.53) 40-59 years: 1% 60-79 years: 5.5% >80 years: 12.6% Men NR (1.34) Women NR (1.72)		
	2016 -2019	Total 935 (8.8) HFrEF 531 (5.0) HFpEF 404 (3.8)	CODE-AF registry	[R21-2619]
Oman	1992 -1994	Total 1164 (0.52) Men 713 (0.60) Women 451 (0.42)	Prospective survey of native Omani population ≥13 years old	[R20-0206]

The figure below shows the prevalence and incidence of HF worldwide.

SI.Figure 4 Prevalence and incidence of HF worldwide



Data source: [R19-3972]

SI.2.3 Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

HF affects mostly elderly patients. For example, in the UK, according to the results of a retrospective cohort study conducted over the period 2002 to 2014 in 3 992 417 patients age >16 years using EMRs from the CPRD, the mean age (SD) at incident HF diagnosis was 76.7 (SD 12.6) years [R19-3743], see table below.

SI.Table 13 Characteristics of patients with incident HF in the UK

	All patients (n=93 074)	Sex		Socioeconomic status		Time period	
		Female (n=45 647)	Male (n=47 427)	SES 1 (n=18 371)	SES 5 (n=16 270)	2002–04 (n=21 943)	2012–14 (n=20 804)
Age (years)	76.7 (12.6)	79.4 (11.8)	74.0 (12.7)	77.8 (12.1)	74.5 (13.3)	76.5 (12.0)	77.0 (12.9)
Sex							
Women	45 647 (49%)	--	--	8694 (48%)	8278 (52%)	10 889 (50%)	10 163 (50%)
Men	47 427 (51%)	--	--	9510 (52%)	7612 (48%)	10 874 (50%)	10 106 (50%)
Ethnicity*							
White	45 550 (97%)	22 247 (98%)	23 303 (97%)	9108 (98%)	8330 (96%)	10 588 (98%)	13 618 (96%)
Missing data	46 278 (50%)	22 875 (50%)	23 403 (49%)	9096 (50%)	7560 (46%)	11 175 (51%)	6651 (32%)
Systolic blood pressure							
Mean (mm Hg)	133 (21)	134 (21)	131 (21)	132 (20)	132 (21)	137 (24)	130 (19)
Missing data	5195 (6%)	2716 (6%)	2479 (5%)	922 (5%)	1057 (6%)	2601 (12%)	645 (3%)
Diastolic blood pressure*							
Mean (mm Hg)	74 (12)	75 (12)	74 (12)	74 (11)	74 (12)	77 (12)	73 (11)
Missing data	5195 (6%)	2716 (6%)	2479 (5%)	922 (5%)	1057 (6%)	2601 (12%)	645 (3%)
BMI category*							
Underweight	2193 (4%)	1541 (6%)	652 (2%)	389 (4%)	424 (4%)	329 (3%)	592 (4%)
Normal	17 381 (31%)	8413 (33%)	8968 (29%)	3665 (35%)	2967 (29%)	3000 (31%)	4368 (30%)
Overweight	18 786 (34%)	7060 (28%)	11 726 (38%)	3741 (35%)	3220 (31%)	3434 (36%)	4629 (32%)
Obese	17 644 (32%)	8222 (33%)	9422 (31%)	2789 (26%)	3793 (37%)	2910 (30%)	4784 (33%)
Missing data	37 070 (40%)	20 411 (45%)	16 659 (35%)	7787 (42%)	5866 (36%)	12 270 (56%)	6431 (31%)
Smoking*							
No	29 551 (41%)	17 603 (53%)	11 948 (31%)	6394 (46%)	4496 (34%)	5081 (41%)	7023 (41%)
Ex-smoker	32 572 (45%)	11 604 (35%)	20 968 (54%)	6248 (45%)	5838 (45%)	5192 (42%)	7949 (47%)
Yes	9596 (13%)	3929 (12%)	5667 (15%)	1146 (8%)	2755 (21%)	2031 (17%)	2065 (12%)
Missing data	21 355 (23%)	12 511 (27%)	8844 (19%)	4583 (25%)	3181 (20%)	9639 (44%)	3767 (18%)

SI.Table 13 (cont'd) Characteristics of patients with incident HF in the UK

	All patients (n=93 074)	Sex		Socioeconomic status		Time period	
		Female (n=45 647)	Male (n=47 427)	SES 1 (n=18 371)	SES 5 (n=16 270)	2002–04 (n=21 943)	2012–14 (n=20 804)
Comorbidities							
Atrial fibrillation	36 950 (40%)	18 309 (40%)	18 641 (39%)	7711 (42%)	6044 (37%)	6990 (32%)	9460 (45%)
CKD	22 762 (24%)	11 912 (26%)	10 850 (23%)	4325 (23%)	3956 (24%)	1363 (6%)	7542 (36%)
COPD	17 896 (19%)	8199 (18%)	9697 (20%)	2670 (14%)	4343 (27%)	3782 (17%)	4494 (22%)
Diabetes	20 531 (22%)	9363 (21%)	11 168 (23%)	3489 (19%)	4238 (26%)	3893 (18%)	5366 (26%)
Dyslipidaemia	25 958 (28%)	11 516 (25%)	14 442 (30%)	5062 (28%)	4948 (30%)	3361 (15%)	8024 (39%)
Hypertension	62 419 (67%)	32 117 (70%)	30 302 (64%)	12 230 (67%)	11 008 (68%)	11 940 (54%)	15 766 (76%)
Ischaemic heart disease	45 584 (49%)	19 408 (42%)	26 176 (55%)	8745 (48%)	8317 (51%)	10 279 (47%)	10 341 (50%)
Osteoarthritis	40 176 (43%)	23 040 (50%)	17 136 (36%)	7828 (43%)	7186 (44%)	7962 (36%)	10 277 (49%)
3 or more comorbidities	73 610 (79%)	37 338 (82%)	36 272 (76%)	14 188 (77%)	13 236 (81%)	14 876 (68%)	18 040 (87%)

Data are mean (SD) or n (%). Socioeconomic status refers to Index of Multiple Deprivation 2015 quintile, with SES 1 referring to the most affluent and SES 5 to the most deprived socioeconomic quintile. Number of comorbidities refers to any of the 17 conditions investigated.

* Number and percentage of records with missing data are displayed for variables with missing entries. Category percentages refer to complete cases.

In a cohort study conducted in Germany in 2006, which included 6 284 194 patients of whom 109 363 (1.7%) had HF, patients with HF were older (mean age: 71.9 [SD 11.9] years) than the rest of the study population (mean age: 39.0 [SD 20.8] years) [R19-3749].

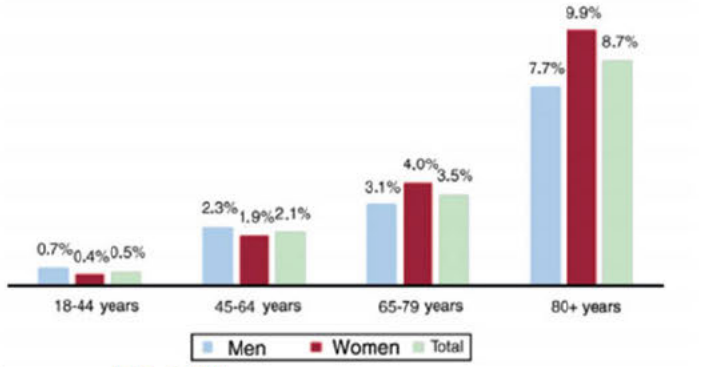
A prospective cohort study conducted in France between 2000 and 2005 reported that the mean age was significantly different between the 2 subtypes of HF, estimated at 75.8 (SD 10.0) years in HFpEF and 71.0 (SD 13.4) years in HFrEF ($p<0.001$) [R19-3968]. In the same study, it was documented that the proportion of patients with HFpEF increased with age; 61% of patients age >75 years were HFpEF patients. These findings were consistent with those of 2 recent non-systematic literature reviews that showed that patients with HFpEF tend to be older than those with HFrEF [R19-0541, R19-3972].

There was a statistically significant difference across genders: men were younger at diagnosis than women, 74.0 (SD 12.7) years and 79.4 (SD 11.8) years, respectively (adjusted difference: -5.51; 95% CI -5.67, -5.35). Over the study period, there was an increase in age at diagnosis from 76.5 (SD 12.0) years in 2002 to 77.0 (SD12.9) years in 2014 (adjusted difference: 0.79 years, 95% CI 0.37, 1.20) [R19-3743].

4 individual studies conducted in France, reported information on gender in HF patients. 2 cross-sectional studies [R19-3999, R19-3968, R19-3967] and 1 prospective cohort [R19-3991], altogether covering the years 2000 to 2013, showed that the proportion of men ranged from 45.0% to 53.8%.

A recent study in Spain based on retrospective analysis of EMR of 1 853 412 patients, showed that HF was rare among individuals younger than 44 years old but became common among elderly particularly among elderly women (SI.Figure 5).

SI.Figure 5 HF prevalence in 2019 in Spain by sex and age range



Data source: [R21-2665]

Data on the ethnic background of HF patients were poorly examined in Europe and Asia-Pacific. In the US, according to the MESA, African-Americans had the highest incidence of HF (4.0 per 1000 PY), followed by Hispanic Americans (3.5 per 1000 PY), Whites (2.4 per 1000 PY) and Chinese Americans (1.0 per 1000 PY) [R14-1824]. A prospective cohort study by Loher et al. in the US described the incidence of HF among Caucasians and African Americans stratified by age categories and sexes (see SI.Table 10) [R08-4693]. In Canada, the Black population was studied in 5 cross-sectional surveys conducted in Ontario, altogether covering the years 1996 to 2007 including 163 797 participants. Although HF risk factors were more frequent in Black individuals, HF prevalence was lower (3.4%) compared to Caucasians (5.0%), South Asians (5.2%), or Chinese (3.2%) [R20-0689].

SI.2.4 Risk factors

Important risk factors for HF include [R13-2139, R19-4001, R19-3997, R19-3990, R19-3974, R19-4000, R19-3970, R19-3991]:

- Age
- Cardiovascular
  - Hypertension
  - Ischaemic heart disease and stroke
  - Myocardial infarction
  - Peripheral disease

  - Coronary disease
  - Arrhythmia and atrial fibrillation
  - Orthostatic hypotension
  - Other CV comorbidities
- Hepatic
- Renal
- Cancer
- Infections
- Skin/allergy/hypersensitivity
- Pulmonary
  - COPD
  - Other pulmonary disease
- Mental illnesses
- Endocrine and metabolic
- Diabetes
  - Dyslipidaemia/hyperlipidaemia
  - Thyroid disease
- Osteoarthritis
- Anaemia
- Obesity
- Insomnia
- Neurological/degenerative disease

SI.2.5 The main existing treatment options

Summary of evidence and key insights

Clinical guidelines for managing HF: overall population

- Clinical guidelines recommend that patients with HFrEF should be treated with an ACE inhibitor (or ARB) and a beta blocker, with or without a MRA, and diuretics should be given as needed [P16-05920, P19-11095, P17-04922, R19-4039, P18-11523, P19-11084].
- Clinical guidelines recommend the use of the ARNI Entresto (sacubitril/valsartan - a combination of the ARB valsartan and the neprilysin inhibitor sacubitril) as a replacement for ARBs or ACE inhibitors in symptomatic HFrEF to further decrease morbidity and mortality [P16-05920, P19-11095, P17-04922, R19-4039, P18-11523].
- Clinical guidelines recommend the use of ivabradine to reduce the risk of HHF in patients with symptomatic HFrEF, in sinus rhythm and a resting heart rate ≥70 bpm, despite treatment with an ACE inhibitor (or ARB) and a beta blocker

(unless contraindicated), with or without a MRA [P16-05920, P19-11095, P17-04922, R19-4039, P18-11523, P19-11084].

- Currently, there are no specific therapies available for the treatment of HFpEF [R19-4042, R19-4041]. Therefore, current recommendations for the treatment of HFpEF include the control of comorbidities including hypertension and the use of diuretics to relieve symptoms in congested patients [P16-05920, P19-11095, P17-04922, R19-4039, P18-11523, P19-11084].

Clinical guidelines for managing HF: patients with T2DM

- Specifically, for patients with T2DM and HF, SGLT-2 inhibitors are recommended to reduce the risk of HHF and prolong life [P18-11523, P18-11501, P18-12233, P18-11398, P19-09415, P18-03381, R20-2910].

Current treatment patterns in clinical practice

- Currently in clinical practice, beta blockers, ARBs, ACE inhibitors, and diuretics remain the mainstay of HF treatment, with a small proportion of patients receiving sacubitril/valsartan (13%) [R19-4049, R19-4063, R19-4040, R19-4064].
- Poor compliance rates are reported with many generic treatments: 53.2% with ACE inhibitors/ARBs, 44.0% with beta blockers, 65.7% with ARAs, and 89.8% with diuretics [R19-4050].

SI.2.6 Natural history of the indicated condition in the population, including mortality and morbidity

The epidemiology of the natural course of HF is well described in the literature. 2 systems of classification were identified in the literature to differentiate the stages and severity of HF in patients. First, the NYHA proposed the following classification:

i) Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnoea, or palpitation.
ii) Class II: Slight limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
iii) Class III: Marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnoea.
iv) Class IV: Any physical activity causes discomfort. Symptoms of heart failure may be present even at rest. Discomfort increases with any physical activity.

Another widely used staging system of HF is based on the AHA/ACC:

i) Stage A: Patients at high risk of developing HF because of the presence of a condition strongly associated with the development of HF.
ii) Stage B: Patients with structural heart disease that is strongly associated with the development of HF but without HF signs or symptoms.

iii) Stage C: Patients with current or prior symptoms of HF associated with underlying structural heart disease.

iv) Stage D: Patients with advanced structural heart disease and refractory symptoms of HF requiring specialised interventions.

According to a meta-analysis, patients with ALVD had a higher risk of progressing to HF [R19-3974]. The absolute risk of progression to HF was 84 per 1000 PY (95% CI 40, 128) in patients with ALVSD and 28 per 1000 PY (95% CI 19,37) in those with ALVDD. According to another meta-analysis, the pooled risk of all-cause hospital readmission or mortality within 90 days after the index HF hospitalisation was increased by several factors: diabetes mellitus (RR 1.18; 95% CI 1.10, 1.27), ischaemic heart disease (RR 1.25; 95% CI 1.08, 1.44), myocardial infarction (RR 1.19; 95% CI 1.06, 1.33), CKD (RR 1.33; 95% CI 1.18, 1.50), chronic lung disease (RR 1.16; 95% CI 1.10, 1.22), cerebrovascular disease (RR 1.16; 95% CI 1.10, 1.22), anaemia (OR 1.73; 95% CI 1.28, 2.35), cognitive impairment (RR 1.28; 95% CI 1.14-1.43), peripheral vascular disease (OR 1.35; 95% CI 1.21, 1.50), post-percutaneous coronary intervention (OR 1.64; 95% CI 1.17, 2.31), and post coronary bypass (RR 1.21; 95% CI 1.05, 1.40) [R19-4007].

The mortality in HF patients is well documented in the literature. According to a prospective cohort study conducted in the US that included 1282 patients with incident HF over the period 1987 to 2002, the age-adjusted mortality rate in Caucasian men was 9.4% (95% CI 7.1, 12.4), 19.6% (95% CI 16.2, 23.5) and 41.2% (95% CI 36.9, 45.6) at 30-day, 1-year, and 5-year after an incident HF hospitalisation [R08-4693]. Several studies reported a decrease of mortality in patients with HF over the year. For example, a study including 622 786 elderly with HF (>65 years) among a 5% random sample of Medicare beneficiaries reported that mortality in patients with incident HF decreased between 1993 and 2003 [R19-4006]. These results were also confirmed in a study (sample size 161 131 hospitalised HF patients) conducted in France, based on the French National Hospitalization Database PMSI, which reported a decline in all-cause death throughout the years 2002 to 2012 (from 9.0% in 2002 to 7.8% in 2012) [R19-4006]. The Olmstead study spanning from 2000 to 2010 (sample size 2762 incident HF cases) examined the major causes of deaths among HF patients (all types), HFrEF patients and HFpEF patients [R19-4008]. More than half (54%) of the deaths were attributable to non-CV causes. A meta-analysis (unrestricted geographical scope) published in 2015, reported information on potential prognostic factors in HF patients [R19-4038]. The search strategy spanned from 01 Jan 1990 to 01 May 2013 and 68 studies were identified. Patients with concomitant diabetes mellitus had an increased risk of all-cause mortality (pooled HR 1.34; 95% CI 1.24, 1.46; according to 9 studies) compared to patients without diabetes mellitus. Additionally, the risk of all-cause mortality was increased by 39% in patients with concomitant COPD (pooled HR 1.39; 95% CI 1.21, 1.60; according to 5 studies) compared to patients without COPD. Patients with HF and renal dysfunction also had an increased risk of all-cause mortality (pooled HR 1,52; 95% CI 1.34, 1.71 [R19-4038, R19-4006].

SI.2.7 Important co-morbidities

Most (>90%) patients with HF have at least 1 comorbidity, and 86% have at least 2 comorbidities [R19-4002, R19-3989, R19-3994]. Patients with HFpEF have a higher number of comorbidities compared to patients with HFmEF and HFrEF. Approximately 27.0% to 40.8% of patients with HF also have diabetes, and its presence is associated with an increase in all-cause mortality, CV mortality, and HHF [R19-3977, R19-3975]. Below is a list (non-exhaustive) of important co-morbidities experienced by individuals with HF [R19-3976]:

- Hypertension
- Obesity
- Dyslipidaemia
- Metabolic syndrome
- Diabetes mellitus
- Myocardial infarction
- Peripheral arterial disease
- Cerebrovascular disease (stroke)
- Atrial fibrillation
- Depression
- Sleep apnoea
- Liver dysfunction
- Kidney injury/disease (CKD, ESRD, acute kidney failure)
- Cognitive impairment

SI.3 TYPE 2 DIABETES MELLITUS (ADULTS AND CHILDREN)

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.3.1 Incidence

SI.3.1.1 Children

Recently, Wu et al conducted a systematic review and modelling analysis to collect worldwide estimates of the incidence of T2DM in children and adolescents aged under 20 years at both regional and national levels [R22-2303]. From 9238 identified studies in the literature search, a total of 25 studies met the inclusion criteria and were included (SI.Table 14). It is important to note that there are substantial variations across these studies in terms of study design, diabetes ascertainment, classification of diabetes type, as well as reported incidence rates [R13-3747]. Approximately 41 600 new cases of diagnosed T2DM in

children and adolescents in 2021 worldwide were observed, with nearly one-third of them in the Western Pacific region [R22-2303].

SI.Table 14 shows characteristics of the studies reporting incidence rates T2DM in children and adolescents aged under 20 years identified from the systemic review.

SI.Table 14 Characteristics of the studies reporting incidence rates of T2DM in children and adolescents aged under 20 years identified from the systemic review

Country or territory	Study region	Sample representation	Ascertainment type	Study year	Age range (years)	Incident cases	PY
Australia [R22-2358]	Western Australia	Regional	Clinical	1990–2012	0–16	135	10 384 615
Austria [R22-2359	Whole nation	National	Clinical	2017	0–14	8	1 263 740
Bangladesh [R07-1216]	Dhaka District	Regional	Clinical	2018	0–19	29	5 087 719
Canada [R12-3066]	Whole nation	National	Clinical	2006–2008	0–17	227	14 717 870
Mainland China [R19-2683]	Zhejiang province	Regional	Clinical	2013	5–19	105	2 900 552
Fiji [R22-2450]	Whole nation	National	Clinical	2001–2012	0–14	13	3 023 256
Finland [R18-3622]	Whole nation	National	Clinical	1992–1996	15–19	8	1 600 000
Germany [R22-2441]	Saxony state	Regional	Clinical	1999–2008	0–14	5	5 000 000
Hong Kong [R22-2448]	Whole region	National	Clinical	2015	0–19	104	1 188 800
Hungary [R22-2441]	Whole nation	National	Clinical	2016	0–18	92	1 818 413
India [R22-2453]	New Delhi and Chennai	National	Clinical	2011–2012	0–19	41	7 445 000
Iran [R22-2451]	One district in Tehran	Local	Screening	1999–2011	10–19	22	24 237

SI.Table 14 (cont'd) Characteristics of the studies reporting incidence rates of T2DM in children and adolescents aged under 20 years identified from the systemic review

Country or territory	Study region	Sample representation	Ascertainment type	Study year	Age range (years)	Incident cases	PY
Japan [R22-2452]	Tokyo	Local	Screening	2015	6–15	5	322 832
Kuwait [R22-2439]	Whole nation	National	Clinical	2011–2013	0–14	32	1 252 434
Mexico [R22-2445]	Whole nation	National	Clinical	2013	10–14	19	11 280 718
New Zealand [R22-2446]	Auckland	Local	Clinical	2009–2015	0–14	52	2 888 888
Qatar [R22-2440]	Whole nation	National	Clinical	2012–2016	0–14	45	1 551 724
Sweden [R12-3057]	Kronoberg	Local	Clinical	1998–2001	0–19	4	129 032
Taiwan [R10-0746]	Whole region	National	Screening	1999	6–18	186	2 862 083
United Kingdom [R22-2442]	Whole nation	National	Clinical	2015	0–16	94	13 008 432
United States [R22-2443]	Washington, Ohio, South Carolina, Colorado, and California	National	Clinical	2014–2015	10–19	355	2 575 000
US Virgin Islands [R22-2449]	Whole nation	National	Clinical	2001–2010	0–19	32	333 333

The incidence and prevalence of youth-onset T2DM vary by ethnicity and other factors. Populations with high incidence and prevalence of T2DM in youth also have higher risk of T2DM among adults. The highest incidence rates of T2DM in youth have been reported from Canadian First Nations, American Indian and Navajo nation, Australian Aboriginal and Torres Strait Islander, and African American populations (31-94 per 100 000 per year) [R22-2443, R22-2358, R22-2479], whereas youth from non-Hispanic Caucasian populations, such as those in Europe and the US had the lowest incidence rates (0.1-0.8 per 100 000 per year) (SI.Figure 6) [R21-3798, R22-2444, R22-2442].

SI.Figure 6 Reported incidence of T2DM in youth ranked by region and ethnicity (year)

Data source: IDF Diabetes Atlas 2021 – 10th edition [R21-3798]

China, India, and US are estimated to have the largest number of children and adolescents with incident T2DM [R22-2303].

SI.Table 15 Incident T2DM in children and adolescents

Rank	Country	Number of incident cases (in 1000)
1	China	7.35
2	India	3.97
3	United States of America	2.85
4	Brazil	1.54
5	Nigeria	1.43
6	Indonesia	1.33
7	Mexico	1.19
8	Egypt	1.16
9	Pakistan	0.88
10	Russian Federation	0.65

Data source: [R22-2303]

SI.3.1.2 Adults

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.

The National Diabetes Statistics Report (2017) [R18-0649], a periodic publication of the CDC, provides periodic updated statistics on diabetes in the US. The estimates in the report were derived from various data systems of the CDC, HIS, AHRQ, the Census Bureau, and published studies. Estimated percentages and total number of people with diabetes were derived from sources, such as the NHANES, NHIS, and USDSS. In 2015, an estimated 1.5 million new cases of diabetes (6.7 per 1000) were diagnosed among adults aged 18 years or older. More than half of these new cases were among adults aged 45 to 64 years, and the numbers were approximately equal for men and women.

SI.Table 16 Estimated incidence of diabetes among adults aged ≥18 years, US, 2015

Characteristic	No. in thousands (95% CI)[a]	Rate per 1000 (95% CI)[b]
Total	1540 (1402-1658)	6.7 (6.2-7.3)
Age in years		
18-44	355 (289-420)	3.1 (2.6-3.8)
45-64	809 (714-905)	10.9 (9.6-12.2)
≥ 65	366 (310-422)	9.4 (8.0-10.9)
Sex		
Women	787 (694-880)	6.8 (6.0-7.6)
Men	743 (645-840)	6.7 (5.9-7.7)

[a] Numbers for subgroups may not add up to the total due to rounding.

[b] Rates are crude, not age-adjusted.

Data source: 2013-2015 NHIS, 2011-2014 NHANES, and 2015 US Census Bureau data. The National Diabetes Statistics Report 2017 [R18-0649]

Non-Hispanic Blacks (9.0 per 1000 persons) and people of Hispanic origin (8.4 per 1000 persons) had a higher age-adjusted incidence compared to non-Hispanic Whites (5.7 per 1000 persons) during 2013 to 2015.

SI.Table 17 Age-adjusted incidence of diagnosed diabetes among adults aged ≥18 years, US, 2013-2015

Characteristic	Rate per 1000 (95% CI)
Race/Ethnicity	
Asian, non-Hispanic	6.0 (4.2-8.6)
Black, non-Hispanic	9.0 (7.4-10.9)
Hispanic	8.4 (7.2-9.8)
White, non-Hispanic	5.7 (5.0-6.4)

Data source: 2013-2015 NHIS and 2015 US Census Bureau data. The National Diabetes Statistics Report 2017 [R18-0649]

The 2011 Public Health Agency of Canada report, *Diabetes in Canada: Facts and figures from a public health perspective* [R18-2223], reported that over 200 000 Canadians (6.3 new cases per 1000 individuals) were diagnosed with diabetes for the first time in 2008/2009. These estimates are based on data from the CCHS. Males (6.8 new cases per 1000 persons) had higher overall incidence rates than females (5.7 new cases per 1000 persons). The incidence rates of diabetes rise steeply after age 40 among both sexes, peaking in the 70 - 74-year age groups. Almost half of incident cases of diabetes in 2008/2009 were aged between 45 and 64. According to the CCHS survey data based on the same age group, among those who self-reported having diabetes, 83.3% were of unhealthy weight (including 47.5% obese) compared to 57.8% with unhealthy weight (including 19.1% obese) among those

without diabetes. This suggests that obesity was a major contributor to diabetes in that age group.

Sharma et al [R18-2264] quantified trends in the incidence T2DM using electronic health records in the THIN primary care database, in the UK. They analysed longitudinal health records between 2000 and 2013. Incidence was classified as the index date for T2DM diagnosis, and refers to the first record of T2DM to appear in a patient's electronic primary care record in the THIN database. They observed that the incidence of T2DM increased from 3.69 per 1000 PYAR (95% CI 3.58-3.81) in 2000 to 3.99 per 1000 PYAR (95% CI 3.90-4.08) for men; and from 3.06 per 1000 PYAR (95% CI 2.95-3.17) to 3.73 per 1000 PYAR (95% 3.65-3.82) in 2013 for women. Incidence peaked in 2004 for both men and women: 4.80 per 1000 PYAR (95% CI 4.70-4.90) and 4.28 per 1000 PYAR (95% CI 4.19-4.38), respectively. In general, it was found that incidence increased with age, peaking between 70 and 79 years. Between ages 10 and 40 years, the incidence was higher in females. However, after the age of 40 years, the crude incidence rate became higher among men. The researchers stated that crude and adjusted incidence rates were similar.

Norhammar et al (2016) [R18-2261] performed a population-based study in Sweden, between 2006 and 2013, to estimate the incidence, prevalence and mortality of T2DM requiring glucose-lowering treatment. Analysis was based on data on patient with T2DM who filled a prescription for any glucose-lowering drug during the period 2006-2013. Data sources used were the Swedish Prescribed Drug Register, Swedish Nation Patient Register and Cause of Death Register. They found that during the study period, the incidence remained relatively stable.

SI.Table 18 Crude of T2DM in the Swedish population

	2006	2007	2008	2009	2010	2011	2012	2013	Change (%) 2006-2013	*P* for trend
Incidence, n	34 020	29 261	31 226	30 966	33 332	31 853	32 411	30 620	-10.0	0.87
Incidence per 100 000	460	393	417	410	439	418	424	399	-13.3	0.45

Data source: [R18-2261]

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

SI.Table 19 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.

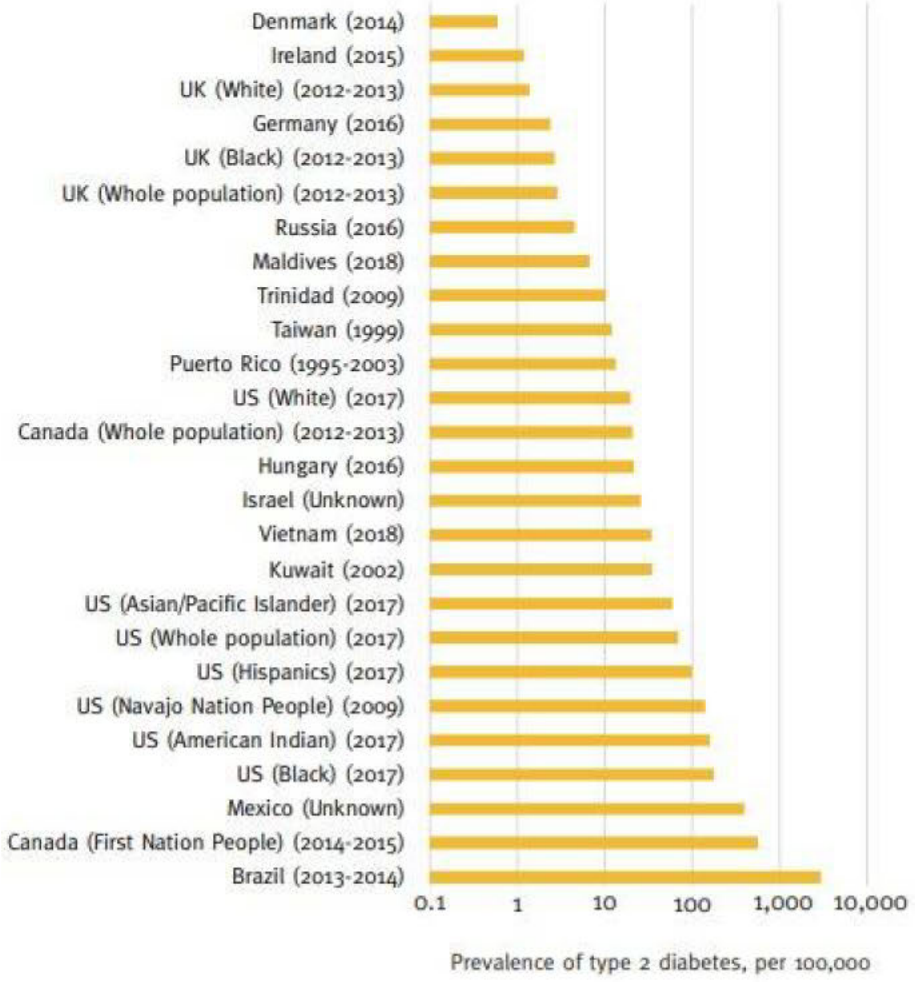
Data source: [R17-3431]

SI.3.2 Prevalence

SI.3.2.1 Children

Prevalence estimates of T2DM were reported to be the highest in youth from Brazil and Mexico, as well as indigenous populations in the US and Canada, and among Black populations in the Americas (160–3300 per 100 000) [R22-2481, R22-2482, R22-2480] and the lowest in populations in Europe (0.6 to 2.7 per 100 000) 26–27 (SI.Figure 7) [R21-3798].

SI.Figure 7 Reported prevalence of T2DM in youth ranked by region and ethnicity (year)



Data source: IDF Diabetes Atlas 2021 – 10th edition [R21-3798]

SI.3.2.2 Adults

According to the National Diabetes Statistics Report (2017) [R18-0649], an estimated 9.4% of the US population (30.3 million people across all ages) had diabetes in 2015. This total included 30.2 million adults aged 18 years or older (12.2% of all US adults), of which 7.2 million (23.8%) were not aware of or did not report have diabetes. The percentage of adults with diabetes increased with age, reaching a peak of 25.2% among those aged 65 years or older (see table below). The number of cases of diagnosed diabetes roughly tripled in the US during the past 2 decades.

SI.Table 20 Estimated number and percentage of diagnosed and undiagnosed diabetes among adults aged ≥18 years, US, 2015

Characteristic	Diagnosed diabetes No. in millions (95% CI)[a]	Undiagnosed diabetes No. in millions (95% CI)[a]	Total diabetes No. in millions (95% CI)[a]
Total	**23.0 (21.1-25.1)**	**7.2 (6.0-8.6)**	**30.2 (27.9-32.7)**
Age in years			
18-44	3.0 (2.6-3.6)	1.6 (1.1-2.3)	4.6 (3.8-5.5)
45-64	10.7 (9.3-12.2)	3.6 (2.8-4.6)	14.3 (12.7-16.1)
≥ 65	9.9 (9.0-11.0)	2.1 (1.4-3.0)	12.0 (10.7-13.4)
Sex			
Women	11.7 (10.5-13.1)	3.1 (2.4-4.1)	14.9 (13.5-16.4)
Men	11.3 (10.2-12.4)	4.0 (3.0-5.5)	15.3 (13.8-17.0)
	Percentage (95% CI)	**Percentage (95% CI)**	**Percentage (95% CI)**
Total	**9.3 (8.5-10.1)[b]**	**2.9 (2.4-3.5)[b]**	**12.2 (11.3-13.2)[b]**
Age in years			
18-44	2.6 (2.2-3.1)	1.3 (0.9-2.0)	4.0 (3.3-4.8)
45-64	12.7 (11.1-14.5)	4.3 (3.3-5.5)	17.0 (15.1-19.1)
≥ 65	20.8 (18.8-23.0)	4.4 (3.1-6.3)	25.2 (22.5-28.1)
Sex			
Women	9.2 (8.2-10.3)	2.5 (1.9-3.2)	11.7 (10.6-12.9)
Men	9.4 (8.5-10.3)	3.4 (2.5-4.6)	12.7 (11.5-14.1)

[a] Numbers for subgroups may not add up to the total due to rounding.

[b] Data are crude, not age adjusted.

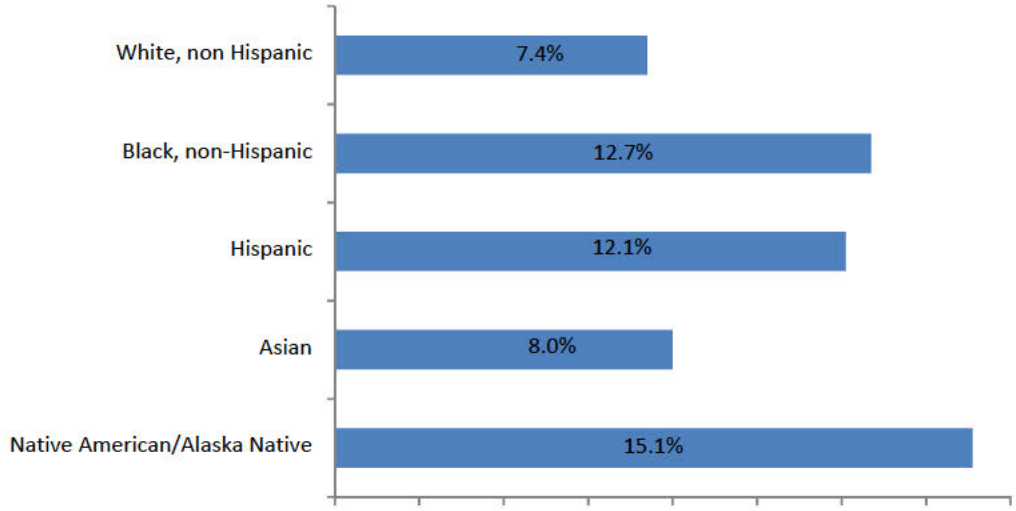
Data source: 2011–2014 NHANES and 2015 US Census Bureau data. The National Diabetes Statistics Report (2017) [R18-0649]

Among the estimated 23.1 million people (7.2% of the population) with diagnosed diabetes, 132 000 were children and adolescents younger than age 18 (0.18% of the population). About 5% of people with diabetes in the US are estimated to have T1DM. Much like global prevalence estimates, diabetes prevalence in the US varies considerably by geographic region in the US, with age adjusted prevalence of diagnosed diabetes (2013) among adults ≥20 years, approximately 2 to 3 times as high in the highest quintile of counties than the lowest quintile. The median age-adjusted county level prevalence of diagnosed diabetes was 9.4%, with a range of 3.8% to 20.8%. [United States Diabetes Surveillance System, website cdc.gov/diabetes/atlas/countydata/atlas.html0]. Counties in the southern and Appalachian regions of the US tended to have the highest prevalence of diagnosed diabetes. The 14 US States with the highest prevalence are: Mississippi (13.6%), West Virginia (12.5%), Kentucky (12.1%), Alabama (12.0%), Louisiana (11.8%), Tennessee (11.4%), Arkansas (11.2%), Texas (11.2%), Georgia (10.7%), Oklahoma (10.7%), Indiana (10.5%),

South Carolina (10.5%), New Mexico (10.5%), and Missouri (10.2%). The percentages are age-adjusted to the 2000 US standard population.

Additionally, prevalence varied considerably by race/ethnicity in the US. Native American/Alaska Natives had the highest prevalence (15.1%) of diagnosed diabetes for both men (14.9%) and women (15.3%). Prevalence varied by region, from 6.0% among Alaska Natives to 22.2% among Native Americans in the Southwest. The figure below shows the percentage of adults with diagnosed diabetes, by race and ethnicity.

SI.Figure 8 Percentage of adults with diagnosed diabetes, by race and ethnicity, 2013-2015



Notes: Percentages are age-adjusted to the 2000 US standard population. Figure adapted from the National Diabetes Statistics Report, 2017.
Data sources: 2013–2015 NHIS and 2015 Indian Health Service National Data Warehouse (Native American/Alaska Native data).

The IDF Diabetes Atlas version 10 (2021) [R22-1190] reported approximately 537 million people worldwide, or 10.5% of adults 20-79 years, are estimated to have diabetes. In higher income countries, approximately 87-91% of people with diabetes have type 2, and 7% - 12% are estimated to have type 1 [R18-2262, R18-2265].

The estimates of the total diabetes prevalence, published in the 2017 IDF Diabetes Atlas, 8th Edition, show that the estimated prevalence of T2DM varies worldwide [R22-1190]. The regional, age-adjusted comparative diabetes prevalence estimates for adults (20-79 years) demonstrated the highest prevalence in Middle East and North Africa (18.1%), followed by North America and Caribbean (11.9%), South-East Asia (10.0%), the Western Pacific (9.9%), South and Central America (8.2%), Europe (7.0%), and Africa (5.3%). 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 [R17-0809]. Much of the variation in the crude prevalence of diabetes mellitus worldwide is attributed to varying economic status, lifestyle factors, age distribution, and ethnicities in different countries. The table below presents the top 10

countries or territories with the highest number of adults, 20-79 years old, with diagnosed diabetes, as reported in the IDF Diabetes Atlas, version 10, 2021.

SI.Table 21 Top 10 countries or territories with the highest number of adults, 20-79 years old, with diagnosed diabetes

Rank	Country/territory	Number of people with diabetes
1	China	140.9 million
2	India	74.2 million
3	Pakistan	33.0 million
4	United States	32.2 million
5	Indonesia	19.5 million
6	Brazil	15.7 million
7	Mexico	14.1 million
8	Bangladesh	13.1 million
9	Japan	11.0 million
10	Egypt	10.9 million

Data source: [R22-1190]

The 59 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. The number of people with diabetes in this region is estimated to be 61 million, representing 9.2% of the population aged 20-79 years, including 21.9 million undiagnosed cases. While the Europe Region has the third lowest crude (and second lowest age adjusted) diabetes prevalence rate compared to the 6 other IDF regions, there are several countries with relatively high diabetes prevalence rates.

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 22 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.3.3 Demographics of the population in the authorised indication and risk factors for the disease

SI.3.3.1 Demographics

SI.3.3.1.1 Children

Evidence suggests that T2DM in youth is different not only from T1DM but also from T2DM in adults and has unique features, such as a more rapidly progressive decline in β-cell function and accelerated development of diabetes complications [R22-2360, R22-1501]. Long-term follow-up data from the TODAY study showed that a majority of individuals with T2DM diagnosed as youth had microvascular complications by young adulthood [R22-2483]. T2DM disproportionately impacts youth of ethnic and racial minorities and can occur in complex psychosocial and cultural environments, which may make it difficult to sustain healthy lifestyle changes and self-management behaviours [R22-2360, R22-2484, R22-2485,

R22-2486]. Additional risk factors associated with T2DM in youth include adiposity, family history of diabetes, female sex, and low socioeconomic status [R22-1501].

SI.3.3.1.2 Adults

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

SI.Table 23 Multicentre study of T2DM in 8 European countries, March 2009 to December 2010

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

Data source: [R14-5420]

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

SI.Table 24 Characteristics of T2DM patients enrolled in the Edinburgh Type 2 Diabetes Study, UK (Scotland), 2006 to 2007

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

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

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

SI.3.4 Risk factors

SI.3.4.1 Children

T2DM disproportionately impacts youth of ethnic and racial minorities and can occur in complex psychosocial and cultural environments, which may make it difficult to sustain healthy lifestyle changes and self-management behaviours [R21-3798]. Additional risk factors associated with T2DM in youth include adiposity, family history of diabetes, female sex, greater BMI, membership of ethnic minority, puberty (mean age of diagnosis is 13.5 years), and low socioeconomic status [R22-1501, R22-2303, R22-2360]. The common link among these risk factors is insulin resistance, which plays a pivotal role in the pathophysiology of T2DM. Both insulin resistance and β-cell failure are present in the fully established diabetes state [R22-2360].

SI.3.4.2 Adults

According to the consensus statement on T2DM prevention, issued in 2007 by the IDF [R07-1222] and the 2017 ADA statement "Standards of Medical Care in Diabetes" [R17-0809], 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, R17-0809]:

- 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

- Polycystic ovary syndrome
- History of CV disease
- Acanthosis nigricans

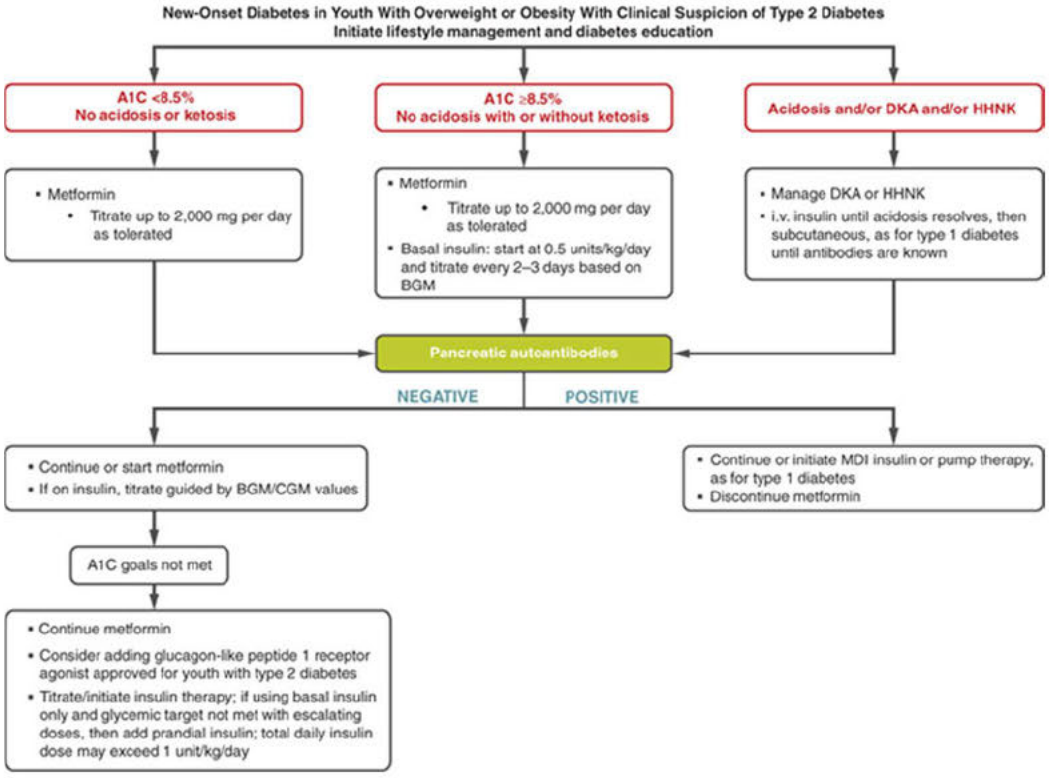
Additionally, particular gene variants, such as the TCF7L2 and, potentially, other loci have been found to confer additional risk for T2DM [R12-5231].

SI.3.5 The main existing treatment options

SI.3.5.1 Children

All youth with T2DM and their families should receive comprehensive diabetes self-management education and support that is specific to youth with T2DM and is culturally appropriate [R22-1501]. The figure below shows the most recent ADA recommendation for the management of new-onset diabetes in youth with overweight or obesity with clinical suspicion of T2DM [R22-1501].

SI.Figure 9 Management of new-onset diabetes in youth with overweight or obesity with clinical suspicion of T2DM



Management of new-onset diabetes in youth with overweight or obesity with clinical suspicion of T2DM.
A1C 8.5% = 69 mmol/mol. Adapted from the ADA position statement "Evaluation and Management of Youth-Onset Type 2 Diabetes".

Data source: [R22-1501]

SI.3.5.2 Adults

The following agents are currently approved in various countries for the treatment of T2DM. Findings from recent CVOTs, providing additional data on CV and renal outcomes in patients with T2DM with CVD or at high risk for CVD are included where applicable [P22-00273].

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
Prominent members of this group are rosiglitazone and pioglitazone. These increase tissue insulin sensitivity by affecting gene expression (peroxisome proliferator-activated receptor gamma) alpha-glucosidase inhibitors (acarbose and miglitol), which interfere with absorption of some glucose containing nutrients, reducing (or at least slowing) the amount of glucose absorbed. 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. DPP-4 inhibitors investigated in CVOTs include saxagliptin (SAVOR-

TIMI53) [R13-3903], alogliptin (EXAMINE) [R13-3902], sitagliptin (TECOS) [R15-3017], and linagliptin (CARMELINA, CAROLINA) [P18-10865, P19-08499] with inclusion criteria ranging from high cardiovascular risk to known CVD with median follow-up of 1.5 to 3 years (up to a median of 6.3 years in the Carolina study with linagliptin). DPP-4 inhibitors showed no increase in MACE, thus demonstrating CV safety in these trials. There was also no reduction in MACE. There are concerns for increasing the risk of HF with saxagliptin but not with other DPP-4 inhibitors [R16-2244, P16-02208].

GLP-1 mimetics
The GLP-1 analogues (e.g. exenatide, liraglutide, semaglutide) increase insulin output from the β-cells among other effects. 7 GLP-1RAs have completed CVOTs and most have indications for CV risk reduction: lixisenatide (ELIXA) [R16-1123], liraglutide (LEADER) [R17-1732, R21-4493], semaglutide (SUSTAIN-6, PIONEER-6) [R18-3864, R22-2321], exenatide (EXSCEL) [R18-3866], albiglutide (HARMONY) [R18-3867], dulaglutide (REWIND) [R22-2319], and efpeglenatide (AMPLITUDE-O) [R22-2337]. Established atherosclerotic CVD at baseline ranged from 31% to 100% of patients. GLP-1RAs decreased weight (0.8-4 kg), and systolic BP (0.8-2.6 mm Hg) over 2.1 to 3.8 years. Although lixisenatide, exenatide, and oral semaglutide were non-inferior to standard care, liraglutide, semaglutide, albiglutide, dulaglutide, and efpeglenatide showed a statistically significant 12% to 27% MACE reduction. This reduction was driven by fewer cardiovascular deaths with liraglutide, less MI with albiglutide, and fewer strokes with injectable semaglutide and dulaglutide. In meta-analyses, GLP-1RAs reduced the risk of 3-point MACE (10%–12%), cardiovascular mortality (12%–13%), all-cause mortality (12%), MI (6%–9%), and stroke (13%–14%) [R22-2334, P22-05206]. There was no significant effect on HHF. Gastrointestinal disturbances and increased heart rate are common GLP-1RA side effects [P22-00273].

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.

SGLT-2 inhibitors investigated in CVOTs include empagliflozin (EMPA-REG OUTCOME) [P15-09840, P16-06807], canagliflozin (CANVAS) [R17-3389], dapagliflozin (DECLARE-TIMI 58) [R19-2814], ertugliflozin (VERTIS-CV) [R22-2330] and sotagliflozin (SCORED and SOLOIST-WHF) [R22-2335, R22-2336]. Established ASCVD at baseline ranged from 41% of patients in CANVAS, to all patients in EMPA-REG OUTCOME and VERTIS-CV trials. SGLT-2 inhibitors lowered SBP (2-3.9 mmHg), and weight (1.0-2.8 kg) compared with placebo over 1 to 4 years.

EMPA-REG OUTCOME and CANVAS both showed a significant 14% lower risk of MACE [P15-09840, R17-3389]. MACE reduction with empagliflozin was primarily driven by a

significant (38%) reduction in CV death. In CANVAS, none of the individual MACE components (CV death, MI, or stroke) was significantly reduced except in the established ASCVD subgroup [P15-09840, R17-3389]. CREDENCE established the MACE benefit of canagliflozin in those with diabetes, CKD, and proteinuria [R19-1356]. DECLARE-TIMI 58 and VERTIS-CV did not demonstrate a significant MACE reduction (3%–7%) in overall, primary, or secondary prevention cohorts, although there was a trend toward benefit in secondary prevention in DECLARE-TIMI 58 [R19-2814]. CANVAS did not show MACE benefit in the primary prevention sub-cohort either [R17-3389].

The SGLT-2 inhibitor trials have shown a congruently lower risk (27%–35%) of HHF [P15-09840, R17-3389, R19-2814, R22-2330]. In magnitude, this is the largest CV benefit of SGLT-2 inhibitors. HHF was reduced more in those with CVD but appeared independent of baseline HF. DAPA-HF and EMPEROR-Reduced confirmed reduction in HHF and CV death in patients with pre-existing HF with or without diabetes [R19-3125, P20-07681]. EMPEROR-Preserved [P21-08234]) showed results similar to EMPEROR-Reduced, thereby demonstrating CV benefit (composite primary endpoint of HHF and CV mortality) of empagliflozin independent of LVEF.

Meta-analyses of CVOTs (excluding ertugliflozin and sotagliflozin) revealed that SGLT-2 inhibitors reduced MACE (11%), CV mortality or HHF (23%), all-cause mortality (15%), MI (11%), and CV mortality (16%) with no effect on stroke [P22-05206]. The 3-point MACE, MI, and CV mortality benefits were only reduced among those with established ASCVD, whereas the HHFs were reduced independent of baseline ASCVD or HF [P22-05206]. Real-world observational studies have largely shown similar findings of reduced HHF and CV mortality [c38709052-02].

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 2022 ADA statement "Standards of Medical Care in Diabetes" recommends "individualised medical nutrition treatment as needed to achieve treatment goals". The daily intake of alcohol should be limited

to a moderate amount (1 drink per day or less for adult women and 2 drinks per day or less for adult men). The guideline references the US Department of Health and Human Services' physical guidelines suggesting that adults over age 18 years engage in at least 150 min per week of moderate-intensity physical activity (50% to 70% of maximum heart rate), or 75 min per week of vigorous-intensity, or an equivalent combination of the two, spread over at least 3 days per week with no more than 2 consecutive days without exercise [R17-0809].

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

SI.3.6 Natural history of the indicated condition in the population, including mortality and morbidity

SI.3.6.1 Children

The incidence of T2DM is extremely low among pre-pubertal children but rises gradually at puberty, likely due to hormonal changes and insulin resistance associated with puberty [R21-3798].

Obesity is an important modifiable risk factor for T2DM. However, some populations that have a low prevalence of childhood obesity, such as East Asians, report higher incidence rates of youth-onset T2DM than populations with a greater burden of childhood obesity. Genetic predisposition, disparities in socio-economic status, access to healthcare and cultural practices across people of different ethnic backgrounds or countries may also contribute to differences in the risk of youth onset T2DM [R21-3798].

SI.3.6.2 Adults

According to the IDF Diabetes Atlas version 10 (2021) [R22-1190], excluding the mortality risks associated with the COVID-19 pandemic, approximately 6.7 million people aged between 20 and 79 years were estimated to have died as a result of diabetes or its complications in 2021. Diabetes accounted for 12.2% of global all-cause mortality among people in this age group. Approximately 32.6% of deaths due to diabetes among the 20-79 age group are in people under the age of 60.

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 CV 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 normo-albuminuria, the hazard ratio for death among those younger than 55 years of age with a glycated haemoglobin level of 6.9% or less, as compared

with controls, was 1.60 (95% CI, 1.40 to 1.82); the corresponding hazard ratio among patients 75 years of age or older was 0.76 (95% CI, 0.75 to 0.78), and patients 65 to 74 years of age also had a significantly lower risk of death (hazard ratio, 0.87; 95% CI, 0.84 to 0.91).

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

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

Data source: [R13-2549]

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

SI.Table 26 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.3.7 Important co-morbidities

SI.3.7.1 Children

Youth-onset T2DM has a unique phenotype and physiology characterised by poorer glycaemic trajectory, higher metformin monotherapy failure rates, and more rapid β-cell functional decline than that seen in adults with T2DM. As compared with T1DM, youth with T2DM are more likely to have or develop other cardiometabolic risk factors, such as high blood pressure, elevated triglycerides, and central obesity. The prevalence of some microvascular complications is 2- to 3-fold higher in youth with T2DM than those with T1DM of a similar age. Compared to the state populations of similar age, sex, and race, excess mortality was also observed in patients with T2DM diagnosed before age 20 years from the SEARCH for Diabetes in Youth study in USA [R22-3833]. The presence of advanced complications during the most productive time of life is more likely to occur given the early onset of T2DM. This has significant impact on individuals, families and communities, and places an additional strain on healthcare systems. Furthermore, the development of T2DM during reproductive years may amplify intergenerational risk for early onset T2DM. While multination surveillance of T1DM is already well established,

surveillance of youth-onset T2DM is not. Therefore, a strong call must be made for the collection of trend data to assess the global burden of T2DM in youth [R21-3798].

Long term follow-up data from the TODAY study showed that a majority of individuals with T2DM diagnosed as youth had microvascular complications by young adulthood [R22-1501].

SI.3.7.2 Adults

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

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

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ABBREVIATIONS

A1C	Glycated haemoglobin
ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
ACEi	Angiotensin-converting enzyme inhibitor
ACR	Albumin-creatinine ratio
ADA	American Diabetes Association
ADR	Annual Data Report
AER	Albumin excretion rate
AF	Atrial fibrillation
AHA	American Heart Association
aHR	Adjusted hazard ratio
AHRQ	Agency for Healthcare Research and Quality
ALVD	Asymptomatic left ventricular dysfunction
ALVDD	Asymptomatic left ventricular diastolic dysfunction

ALVSD	Asymptomatic left ventricular systolic dysfunction
AMI	Acute myocardial infarction
AMPLITUDE-O	Study acronym; A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Effect of Efpeglenatide on Cardiovascular Outcomes in Type 2 Diabetes Patients at High Cardiovascular Risk
ARA	Aldosterone receptor antagonists
ARB	Angiotensin receptor blocker
ARIC	Study acronym; The Atherosclerosis Risk in Communities cohort study
ARNI	Angiotensin receptor-neprilysin inhibitor
ASCVD	Atherosclerotic cardiovascular disease
BGM	Blood glucose monitoring
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CAD	Coronary artery disease
CANVAS	Study acronym; Canagliflozin Cardiovascular Assessment Study
CARDIA	Study acronym; Coronary Artery Risk Development in Young Adults
CaReMe	Study acronym; CArdioRenal and MEtabolic Study
CARMELINA	Study acronym; Cardiovascular and Renal Microvascular Outcome Study With Linagliptin
CAROLINA	Study acronym; Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes
CCHS	Canadian Chronic Disease Surveillance System
CDC	Centers for Disease Control and Prevention
CHD	Coronary heart disease
CHF	Chronic heart failure
CHIRA	China Health Insurance Research
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKD-REIN	Chronic Kidney Disease-Renal Epidemiology and Information Network

CK-NET	China Kidney Disease Network
CODE-AF	Study acronym; COmparison Study of Drugs for Symptom Control and Complication prEvention of Atrial Fibrillation
COPD	Chronic obstructive pulmonary disease
CORTS	China Organ Transplant Response System
COVID-19	Coronavirus disease 2019
CPRD	The Clinical Practice Research Datalink
CREDENCE	Study acronym; Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation
CV	Cardiovascular
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
CVOT	Cardiovascular outcome trial
DAPA-HF	Study acronym; Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure
DBP	Diastolic blood pressure
DECLARE-TIMI 58	Study acronym; Dapagliflozin Effect on Cardiovascular Events trial
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DPP-4	Dipeptidyl-peptidase 4
EF	Ejection Fraction
eGFR	Estimated glomerular filtration rate
eGFRcr	Creatinine-based estimated glomerular filtration rate
eGFRcr-cys	Creatinine- and cystatin C-based estimated glomerular filtration rate
eGFRcys	Cystatin C-based estimated glomerular filtration rate
EHR	Electronic health records (database)
ELIXA	Study acronym; Evaluation of Lixisenatide in Acute Coronary Syndrome
EMPA-REG OUTCOME	Study acronym; Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients – Removing Excess Glucose
EMPEROR-Preserved	Study acronym; Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction

EMPEROR-Reduced	Study acronym; Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction
EMR	Electronic medical record
ESRD	End-stage renal disease
EXAMINE	Study acronym; Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care
EXSCEL	Study acronym; Exenatide Study of Cardiovascular Event Lowering Trial
FFS	Fee-for-service
FPG	Fasting plasma glucose
GBD	Global Burden of Diseases, Injuries, and Risk Factors Study
GFR	Glomerular filtration rate
GI	Gastrointestinal
GIP	Gastric inhibitory polypeptide
GLP-1	Glucagon-like peptide 1
GLP-1RA	Glucagon-like peptide 1 receptor agonist
GoDARTS	Study acronym; Genetics of Diabetes Audit and Research Tayside Scotland registry
GP	General practitioner
GPRD	The General Practice Research Database
HARMONY	Study acronym; Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease
HbA_{1c}	Glycated haemoglobin
HBV	Hepstein Barr virus
HCV	Hepatitis C virus
HD	Hemodialysis
HDL	High density lipoprotein
HF	Heart failure
HFmEF	Heart failure with a mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Hearth failure with reduced ejection fraction
HHF	Hospitalisation for heart failure
HHNK	Hyperosmolar hyperglycaemic non-ketotic syndrome
HIS	Indian Health Service

HIV	Human immunodeficiency virus
HQMS	Hospital Quality Monitoring System
HR	Hazard ratio
HTN	Hypertension
ICD	International Classification of Diseases
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IKEAJ	International Kidney Evaluation Association Japan
IQR	Interquartile range
JNC7	Seventh Joint National Committee
KDIGO	Kidney Disease: Improving Global Outcomes
KEEP	Study acronym; The Kidney Early Evaluation Program
LEADER	Study acronym; Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results study
Look AHEAD	Study acronym; Action for Health in Diabetes
LVEF	Left ventricular ejection fraction
MA	Medicare Advantage
MACE	Major adverse cardiac effects
MADIABETES	Madrid Diabetes
MESA	Multi-Ethnic Study of Atherosclerosis
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
MS	Multiple sclerosis
NAFLD	Non-alcoholic fatty liver disease
NH	Non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHIS	Nation Health Interview Survey
NR	Not reported
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
OR	Odds ratio
PA	Physical activity

PAD	Peripheral artery disease
PD	Peritoneal dialysis
PIONEER-6	Study acronym; Peptide Innovation for Early Diabetes Treatment 6
PMSI	Programme de Médicalisation des Systèmes d'Information, French National Hospitalization Database
PREDICTOR	Study acronym; Valutazione della PREvalenza di DIsfunzione CardiacaasinTOmatica e di scompenso caRdiaco
PY	Patient-years, person-years
PYAR	Person-years at risk
QOF	Quality and Outcomes Framework
READ	Standard Clinical Terminology System Used in General Practice in the UK
REWIND	Study acronym; Researching Cardiovascular Events With a Weekly Incretin in Diabetes
RR	Relative risk
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAVOR-TIMI53	Study acronym; Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53
SBP	Systolic blood pressure
SCORED	Study acronym; Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk
SD	Standard deviation
SES	Socioeconomic status
SGLT-2	Sodium-dependent glucose co-transporter 2
SOLOIST-WHF	Study acronym; Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure
SU	Sulphonylurea
SUSTAIN-6	Study acronym; Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TCF7L2	Transcription factor 7 like 2
TECOS	Study acronym; Trial Evaluating Cardiovascular Outcomes With

	Sitagliptin
THIN	The Health Improvement Network (database)
TIA	Transient ischemic attack
TODAY	Study acronym; Treatment Options for Type 2 Diabetes in adolescents and Youth
TZD	Thiazolidinedione
uACR	Urine albumin-creatinine ratio
UK	United Kingdom
US(A)	United States (of America)
USDSS	United States Diabetes Surveillance System
USRDS	United States Renal Data System
UTI	Urinary tract infection
VA	Veterans Affairs
VERTIS-CV	Study acronym; Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes trial]

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

The toxic potential of empagliflozin has been fully explored in an extensive non-clinical safety programme including studies of general toxicology, genetic toxicology, carcinogenicity, reproductive and developmental toxicology, and local tolerance.

The acute oral toxicity of empagliflozin was assessed in single dose studies in rodents. Acute toxicity in mice and rats was low as indicated by a lethal dose of >2000 mg/kg.

The repeat-dose toxicity of empagliflozin was evaluated in pivotal studies in CD-1 mice, Wistar (Han) rat strains, and in Beagle dogs for up to 3 months, 6 months, and 12 months, respectively. Toxicokinetic analyses after repeated oral administrations revealed high and dose-related systemic exposure to empagliflozin in all species investigated. Exposure to empagliflozin achieved in pivotal chronic studies in mouse, rat, and dog were up to 62- and 158-fold, 35- and 89-fold, and 240- and 610-fold clinical exposure associated with the 25 mg and 10 mg doses, respectively.

Signs of toxicity were observed at doses far in excess of those recommended for therapy. Across species, most toxicity was consistent with secondary pharmacology related to urinary glucose loss and electrolyte imbalances including decreased body weight and body fat, increased food consumption, diarrhoea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism and gluconeogenesis, urinary changes such as polyuria, and glucosuria. Microscopic changes were consistently observed in kidney some soft and vascular tissues, and included tubular karyomegaly, single cell necrosis, cystic hyperplasia and hypertrophy (mouse), renal mineralisation (rat), and tubular nephropathy and interstitial nephritis (dog). Microscopic evidence of empagliflozin-related renal pharmacology was apparent in some species at approximately 4- and 11-times the clinical AUC exposure of empagliflozin associated with the 25 mg and 10 mg doses, respectively. In the rodent studies, systemic exposure was typically lower in males than in females, but was similar between sexes of dog. In these pivotal general toxicology studies in male mouse, male rat, and dog, the NOAEL for systemic toxicity was 47- and 120-fold, 10- and 25-fold, and 18- and 46-fold exposure associated with the daily therapeutic dose of 25 mg and 10 mg doses, respectively.

Empagliflozin is non-genotoxic as assessed in a standard battery of *in vitro* gene mutation (Ames bacterial mutagenesis) and chromosomal damage (L5178 tk+/- mouse lymphoma) assays and in vivo (rat bone marrow micronucleus) tests for genotoxicity.

Empagliflozin was tested for developmental and reproductive toxicity in rats and rabbits. Fertility and early embryonic development was assessed in rat. Empagliflozin had no adverse

effects on fertility and early embryonic development at doses up to 700 mg/kg, which corresponds to approximately 155- and 393-fold exposure associated with the 25 mg and 10 mg doses, respectively. Empagliflozin administered during the period of organogenesis was not teratogenic in rats or rabbits at exposures which were >48- and 122-fold exposure associated with the 25 mg and 10 mg doses, respectively, or at doses that were not maternally toxic. Doses of empagliflozin causing maternal toxicity in the rat caused the malformation of bent limb bones at exposures approximately 155- and 393-times the clinical dose associated with the 25 mg and 10 mg doses, respectively. Maternally toxic doses in the rabbit caused increased embryofoetal loss at doses approximately 139- and 352-times the clinical dose associated with the 25 mg and 10 mg doses, respectively. In the pre- and postnatal developmental toxicity study, the NOAEL for maternal systemic toxicity and for growth of F1 generation offspring was >16- and 41-fold and 1- and 4-fold exposure associated with the 25 mg and 10 mg doses, respectively. Other SGLT-2 inhibitors have effects on renal development in rats during the period of organogenesis corresponding to the second and third trimesters of pregnancy. Empagliflozin has not been similarly tested.

In pre- and postnatal developmental toxicology studies in rats, body weight gain of offspring was reduced at maternal empagliflozin exposures that are 4- and 11-fold the exposure of the 25 mg and 10 mg therapeutic doses, respectively. No such effect was seen at systemic exposure equal to or 4-times the systemic exposure in humans at the recommended therapeutic doses of 25 mg or 10 mg. There are no studies in humans, but in rat studies empagliflozin has been shown to be excreted at low levels in milk. In a juvenile toxicity study in the rat, when empagliflozin was administered from PND 21 until PND 90, non-adverse, minimal to mild renal tubular and pelvic dilation in juvenile rats was seen only at 100 mg/kg/day, which approximates 11-times the maximum clinical dose of 25 mg based on AUC. These findings were absent after a 13 weeks drug-free recovery period [n00231757-01].

Empagliflozin has been evaluated for dermal sensitisation and dermal and ocular irritation. Empagliflozin is neither a dermal sensitizer nor irritant and is non-irritating to the eyes. Evaluations of photoabsorption spectrum and distribution of ^{14}C-labelled empagliflozin to eye and skin coupled with the results of general toxicology studies revealed no potential for phototoxicity.

Empagliflozin has no immunotoxic or phototoxic potential.

Tissue distribution studies of ^{14}C-empagliflozin in pigmented rats demonstrated that drug-related material was not associated with the melanin-containing tissues in eye or skin.

SII.1.2 Safety pharmacology

In a battery of single dose secondary pharmacodynamic and safety pharmacology studies, empagliflozin had no effects on the central nervous system, hepatic, gastrointestinal, respiratory, or cardiovascular systems. There were no effects in vitro on the hERG potassium ion channel or on the action potential configuration or contractility of the guinea pig papillary muscle. Empagliflozin effects on renal function were directly related to its pharmacological activity.

SII.1.3 Other toxicity-related information or data

Oncogenicity
2-year carcinogenicity studies were performed using CD-1 mice and Wistar (Han) rats. Dose selections were predicated on AUC and MTD considerations. There was no evidence of carcinogenic potential in female mice at doses up to 1000 mg/kg/day, which is approximately 62- and 159-fold clinical exposure associated with the 25 mg and 10 mg doses, respectively. Empagliflozin-related renal adenoma and carcinoma occurred in male mice administered 1000 mg/kg/day, which corresponds to approximately 45- and 113-fold exposure associated with the 25 mg and 10 mg doses in humans, respectively. Research into the mode of action for these renal tumours revealed them to be secondary to several sources of chronic and persistent tubular degeneration [U13-3693-02]. These sources include a natural predisposition of the aged male mouse to renal pathology, exacerbation of background renal tubular dilatation and cystic hyperplasia induced by chronic osmotic diuresis, metabolic stress due to a predominantly oxidative metabolism, production of a cytotoxic metabolite predominant in the male mouse, and consequent exhaustion of tubular epithelial oxidative detoxication. Reparative tubular epithelial cell proliferation is observed in male mice, but not female mice indicating the specificity of the sequence of events for the male CD-1 mouse. Ultimately over the course of 2 years of treatment, these key events lead to a constitutive focal proliferative phenotype and a low incidence of renal tumours appearing late in life. Based on this research the male mouse-specific tumours are considered to be irrelevant for humans: the mode of action for these tumours is dependent on the natural predisposition of the male mouse to renal pathology and a metabolic pathway not reflective of humans. There was no evidence of carcinogenicity in female rats at doses up to 700 mg/kg/day, which corresponds to approximately 72- and 182-fold exposure associated with the 25 mg and 10 mg doses in humans, respectively. Benign vascular tumours (haemangioma) of the mesenteric lymph node was associated with empagliflozin administration in male rats given 700 mg/kg/day, which corresponds to approximately 42- and 105-times the clinical exposure of empagliflozin associated with the 25 mg and 10 mg doses in humans, respectively. These benign tumours are common in the male Wistar (Han) rat and are unlikely to be relevant to humans. Benign testicular interstitial cell tumours were observed in rats of the 300 and 700 mg/kg/day groups, but the incidence was not dose related and there was no evidence of an associated hyperplasia. These tumours are considered secondary to severe body weight loss and to have little, if any, relevance to humans.

Special populations: paediatrics
The available non-clinical data for empagliflozin are considered sufficient to support clinical trials in a paediatric population >2 years of age. The animal models used in the non-clinical development of empagliflozin are considered to cover the stage of development of the intended paediatric population sufficiently. There are no findings in a toxicity study in the juvenile rat that are of specific concern to the paediatric population ≥2 years of age at clinical relevant doses.

Ketone production
SGLT-2 inhibitors may modestly increase the level of ketone bodies in preclinical models as well as in humans without causing acidosis under normal conditions. The insulin independency of SGLT-2 inhibitors to reduce blood glucose levels, via glucosuria, is the

underlying mechanism of an increase of ketone production especially under fasting condition. The diminution in blood glucose levels induced by SGLT-2 inhibitors is associated with a decrease in insulin levels, the activation of glucose hepatic output and an increase of the glucagon/insulin ratio. These conditions alter hepatic metabolism to favour ketone production especially under fasting condition or low carbohydrate diet when the glycogen stores are depleted. Because the ketone production in the liver is fuelled by the fat (free fatty acid) contents in the plasma, the level of ketone bodies in the blood was investigated during re-feeding when fat level increased in plasma while the liver being in a ketogenic state. Under this condition a moderate and transient burst of ketone, above baseline, was observed in non-diabetic rats pre-treated with empagliflozin, fasted 7 h, when the animals were re-fed with chow diet [n00253114-01]. A re-feeding process in empagliflozin pre-treated animals either with a solution containing glucose, fat, or both demonstrated that this transient burst of ketone in blood was provoked only by the fat. However, the presence of glucose with the fat at re-feeding after the fasting period allowed blunting this phenomenon [n00253114-01]. In conclusion, treatment with empagliflozin resulted at re-feeding, after a fasting period, in a modest and transient burst of ketone in the blood according to the fat contained in the diet.

SII.2 REFERENCES

SII.2.1 Published references

Not applicable.

SII.2.2 Unpublished references

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n00253114-01 Effect of empagliflozin on blood ketone level at refeeding after a fasting period. Comparison between refeeding with glucose or fat. 14R018. 25 Oct 2016.

U13-3693-02 Mode-of-action and relevance for empagliflozin-related renal tumours in the mouse carcinogenicity study. 18 Oct 2013.

ABBREVIATIONS

AUC	Area under the curve
hERG	Human ether-a-go-go related gene
MTD	Maximum tolerated dose
NOAEL	No observable adverse effect level
PND	Postnatal day
SGLT-2	Sodium-dependent glucose co-transporter 2

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 of safety analysis sets

SAF/trial	Description	Trials included
Trial 1218-0091	Randomised, placebo-controlled clinical trial in paediatric patients (DINAMO)	1218-0091
Trial 1245-0137	Randomised, double-blind, placebo-controlled clinical trial in patients with chronic kidney disease (EMPA-KIDNEY)	1245-0137
SAF-HF4	Randomised, placebo-controlled clinical trials in patients with HFpEF	1245-0110, 1245-0148 (HFpEF arm), 1245-0167
SAF-HF5[1]	Randomised, placebo-controlled clinical trials in patients with HFrEF	1245-0121, 1245-0168
SAF-43[2]	Randomised, double-blind, placebo-controlled trials in patients with T2DM	1245-0004, 1245-0009, 1245-0010, 1245-0015, 1245-0019, 1245-0020, 1245-0023 (Met only and Met+SU), 1245-0025, 1245-0029, 1245-0033, 1245-0035, 1245-0036, 1245-0038, 1245-0048, 1245-0049, 1245-0107, 1275-0009, 1275-0019, 1276-0010
Pooling CKD+HF+T2DM+PAED[2]	Randomised, placebo-controlled clinical trials across indications (CKD, HF, adult + paediatric T2DM)	1218-0091, 1245-0004, 1245-0009, 1245-0010, 1245-0015, 1245-0019, 1245-0020, 1245-0023, 1245-0025, 1245-0029, 1245-0031, 1245-0033, 1245-0035, 1245-0036, 1245-0038, 1245-0048, 1245-0049, 1245-0107, 1245-0110, 1245-0121, 1245-0137, 1245-0148, 1245-0167, 1245-0168, 1245-0191, 1245-0204, 1275-0009, 1275-0019, 1276-0010

[1] Data from trial 1245-0148 was not available at the time of database lock for the HFrEF submission; the trial is therefore not included in the pooling.

[2] The data of extension trial 1245-0031 are contained in the core trials 1245-0019, 1245-0020, and 1245-0023.

Data source: data on file, SAF-43 Table 31.3.1.1; SAF-HF5(HFrEF) Tables 1.1 and 1.2; SAF-HF4(HFpEF) Tables 1.1 and 1.2; rmp-output-ckd, Tables 15.1.1: 1 and 15.1.1.: 2; rmp-output-paediatric, Table 15.2.1: 2; x1245csap54-060601-study-report-body-final, Table 6.1.1

SIII.1 PAEDIATRIC T2DM INDICATION (TRIAL 1218-0091)

In trial 1218-0091, 53 patients received placebo and 52 patients empagliflozin. The total exposure amounted to 25.0 PY in the placebo group and 23.7 PY in the empagliflozin group. Both treatment groups comprised more female than male patients. With regard to ethnic

origin, the largest proportion of patients in both treatment groups was White, followed by Black. An overview is given in the tables below.

SIII.Table 2 Duration of exposure (trial 1218-0091) - TS

	Placebo		All Empa[1]	
	Patients N (%)	Person-time [PY]	Patients N (%)	Person-time [PY]
Cumulative exposure				
≥0 weeks	53 (100.0)	25.0	52 (100.0)	23.7
≥12 weeks	50 (94.3)	24.7	49 (94.2)	23.6
≥26 weeks	34 (64.2)	17.2	31 (59.6)	15.7

[1] All Empa contains empagliflozin 10 mg/25 mg of trial 1218-0091.

Data source: data on file, rmp-output-paediatric, Table 15.2.2.2: 1

SIII.Table 3 Age group and gender (trial 1218-0091) - TS

Gender/ Age group [years]	Placebo		All Empa[1]	
	Patients N	Person-time [PY]	Patients N	Person-time [PY]
Male				
<65	19	9.3	19	9.0
Female				
<65	34	15.6	33	14.8

[1] All Empa contains empagliflozin 10 mg/25 mg of trial 1218-0091.

Data source: data on file, rmp-output-paediatric, Table 15.2.2.2: 3

SIII.Table 4 Ethnic origin (trial 1218-0091) - TS

Race	Placebo		All Empa[1]	
	Patients N	Person-time [PY]	Patients N	Person-time [PY]
American Indian/Alaska Native	1	0.5	4	1.8
Asian	3	1.4	2	1.0
Black/African American	17	7.4	19	8.8
Native Hawaiian/Pacific Islander	1	0.5	0	0
White	29	14.6	23	10.2
Multiple	1	0.0	4	2.0

[1] All Empa contains empagliflozin 10 mg/25 mg of trial 1218-0091.

Data source: data on file, rmp-output-paediatric, Table 15.2.2.2: 4

SIII.1 INDICATION CKD (TRIAL 1245-0137)

In trial 1245-0137, 3305 patients received placebo and 3304 patients empagliflozin 10 mg. The median observation time up to the end of the follow-up period was about 24 months in both treatment groups, with 98% of participants observed for at least 1 year and 51% for at least 2 years. An overview is given in the table below.

SIII.Table 5 Observational period up to the end of follow-up – RS

	Placebo	Empagliflozin 10 mg	Total
Number of participants, N (%)	3305 (100.0)	3304 (100.0)	6609 (100.0)
Observation time categories, N (%)			
≥8 weeks	3302 (99.9)	3302 (99.9)	6604 (99.9)
≥26 weeks	3283 (99.3)	3283 (99.4)	6566 (99.3)
≥52 weeks	3240 (98.0)	3243 (98.2)	6483 (98.1)
≥78 weeks	2438 (73.8)	2422 (73.3)	4860 (73.5)
≥104 weeks	1674 (50.7)	1681 (50.9)	3355 (50.8)
≥130 weeks	710 (21.5)	728 (22.0)	1438 (21.8)
≥156 weeks	34 (1.0)	33 (1.0)	67 (1.0)
Observation time [months]			
Median (Q1, Q3)	24.33 (18.03, 29.70)	24.37 (18.00, 29.80)	24.33 (18.00, 29.73)
Mean (SD)	23.89 (6.94)	23.94 (6.95)	23.91 (6.95)
Total observation time [years]	6484.6	6495.4	12980.1

Observational time, used for majority of efficacy endpoints, was defined as time from randomisation to the date of the final follow-up visit

Data source: CTR 1245-0137 [c37800399-01], Table 10.5: 1

Median exposure to study medication was about 22 months in both treatment groups, with 91% of participants treated for at least 1 year and 44% for at least 2 years, see table below for further details.

SIII.Table 6 Exposure to study medication – TS

	Placebo	Empagliflozin 10 mg	Total
Number of participants, N (%)	3305 (100.0)	3304 (100.0)	6609 (100.0)
Exposure categories, N (%)			
≥8 weeks	3274 (99.1)	3262 (98.7)	6536 (98.9)
≥26 weeks	3172 (96.0)	3161 (95.7)	6333 (95.8)
≥52 weeks	3007 (91.0)	3011 (91.1)	6018 (91.1)
≥78 weeks	2165 (65.5)	2170 (65.7)	4335 (65.6)
≥104 weeks	1444 (43.7)	1467 (44.4)	2911 (44.0)
≥130 weeks	590 (17.9)	606 (18.3)	1196 (18.1)
≥156 weeks	25 (0.8)	28 (0.8)	53 (0.8)
Duration of exposure [months]			
Median (Q1, Q3)	21.57 (16.73, 28.87)	21.92 (16.87, 28.93)	21.73 (16.80, 28.90)
Mean (SD)	22.06 (8.08)	22.15 (8.15)	22.10 (8.12)
Total exposure [years]	5987.3	6009.8	11997.1

Exposure time was defined as time from date of first intake until date of permanent discontinuation of study medication.
Data source: CTR 1245-0137 [c37800399-01], Table 10.5: 2

SIII.2 INDICATION HFPEF

SAF-HF4 comprised cumulative data of 3160 patients receiving placebo and 3175 patients empagliflozin 10 mg. More than half of the patients in either treatment group were exposed for up to 78 weeks to trial medication. The cumulative patient-time was comparable between treatment groups. An overview of cumulative exposure is given in SIII.Table 7.

Both treatment groups comprised fewer female than male patients. The distribution across age categories was comparable within the respective male and female groups. Further details are given in SIII.Table 8.

With regard to ethnic origin, the largest proportion of patients in both treatment groups was White, followed by Asian. A tabular overview is given in SIII.Table 9.

Presence of diabetes mellitus (at baseline) was comparable between both treatment groups (SIII.Table 10).

SIII.Table 7 Duration of exposure (SAF-HF4) - TS

	Placebo		Empagliflozin 10 mg	
	Patients N (%)	**Person-time [PY]**	**Patients N (%)**	**Person-time [PY]**
Cumulative exposure				
≥0 weeks	3160 (100.0)	5604.9	3175 (100.0)	5639.1
≥12 weeks	2968 (93.9)	5582.6	2996 (94.4)	5618.9
≥26 weeks	2697 (85.3)	5503.3	2728 (85.9)	5541.0
≥52 weeks	2509 (79.4)	5366.1	2526 (79.6)	5389.5
≥78 weeks	1928 (61.0)	4622.1	1913 (60.3)	4603.5
≥104 weeks	1388 (43.9)	3674.0	1380 (43.5)	3667.2
≥156 weeks	308 (9.7)	990.4	303 (9.5)	978.8

Data source: data on file, SAF-HF4(HFpEF), Table 3.1.1.1

SIII.Table 8 Age group and gender (SAF-HF4) - TS

Gender/ Age group [years]	Placebo		Empagliflozin 10 mg	
	Patients N	**Person-time [PY]**	**Patients N**	**Person-time [PY]**
Male				
<65	403	734.1	392	721.2
65 to <75	665	1231.6	685	1219.0
≥75	681	1173.9	682	1207.9
Female				
<65	223	415.2	235	415.3
65 to <75	496	869.6	499	906.7
≥75	692	1180.5	682	1169.0

Data source: data on file, SAF-HF4(HFpEF), Table 3.1.1.3

SIII.Table 9 Ethnic origin (SAF-HF4) – TS

Race	Placebo		Empagliflozin 10 mg	
	Patients N	Person-time [PY]	Patients N	Person-time [PY]
American Indian/Alaska Native	106	198.8	90	172.1
Asian	411	805.4	419	808.8
Black/African American	144	219.4	147	240.4
Native Hawaiian/Pacific Islander	19	34.1	14	28.1
White	2405	4211.6	2442	4287.9
Multiple	75	135.6	60	99.3

ource: data on file, SAF-HF4(HFpEF), Table 3.1.1.4

SIII.Table 10 Diabetes mellitus at baseline (SAF-HF4) – TS

Diabetes mellitus	Placebo		Empagliflozin 10 mg	
	Patients N	Person-time [PY]	Patients N	Person-time [PY]
No	1611	2864.8	1617	2898.4
Yes[1]	1547	2739.6	1556	2740.2

etes mellitus status at baseline comprised T2DM patients only; there were no T1DM patients.
ource: data on file, SAF-HF4(HFpEF), Table 3.1.1.7

SIII.3 INDICATION HFREF

SAF-HF5 comprised cumulative data of 2019 patients receiving placebo and 2018 patients empagliflozin 10 mg. More than half of the patients in either treatment group were exposed for up to 52 weeks to trial medication. The cumulative patient-time was comparable between treatment groups. An overview of cumulative exposure is given in SIII.Table 11.

Both treatment groups comprised fewer female than male patients. The distribution across age categories was comparable within the respective male and female groups. Further details are given in SIII.Table 12.

With regard to ethnic origin, the largest proportion of patients in all treatment groups was White, followed by Asian. A tabular overview is given in SIII.Table 13.

SIII.Table 11 Duration of exposure (SAF-HF5) - TS

	Placebo		Empagliflozin 10 mg	
	Patients N (%)	**Person-time [PY]**	**Patients N (%)**	**Person-time [PY]**
Cumulative exposure				
≥0 weeks	2019 (100.0)	2257.8	2018 (100.0)	2273.9
≥12 weeks	1839 (91.1)	2236.8	1859 (92.1)	2254.6
≥26 weeks	1622 (80.3)	2174.2	1644 (81.5)	2190.9
≥52 weeks	1133 (56.1)	1815.3	1135 (56.2)	1813.3
≥78 weeks	612 (30.3)	1168.3	609 (30.2)	1158.8
≥104 weeks	214 (10.6)	476.4	210 (10.4)	465.7

Data source: data on file, SAF-HF5(HFrEF), Table 3.1.1.1

SIII.Table 12 Age group and gender (SAF-HF5) - TS

Gender/ Age group [years]	Placebo		Empagliflozin 10 mg	
	Patients N	**Person-time [PY]**	**Patients N**	**Person-time [PY]**
Male				
<65	610	699.5	535	603.7
65 to <75	529	604.1	585	670.2
≥75	382	417.1	426	457.9
Female				
<65	177	196.9	187	220.1
65 to <75	156	171.9	156	178.5
≥75	165	168.3	129	143.5

Data source: data on file, SAF-HF5(HFrEF), Table 3.1.1.3

SIII.Table 13 Ethnic origin (SAF-HF5) – TS

Race	Placebo		Empagliflozin 10 mg	
	Patients N	Person-time [PY]	Patients N	Person-time [PY]
American Indian/Alaska Native	25	26.1	16	18.5
Asian	336	430.3	338	439.4
Black/African American	152	159.4	147	154.5
Native Hawaiian/Pacific Islander	7	8.3	8	12.4
White	1434	1562.4	1454	1587.6
Multiple	33	35.8	28	30.3

Data source: data on file, SAF-HF5(HFrEF), Table 3.1.1.4

SIII.Table 14 Diabetes mellitus at baseline (SAF-HF5) – TS

Diabetes mellitus	Placebo		Empagliflozin 10 mg	
	Patients N	Person-time [PY]	Patients N	Person-time [PY]
No	992	1131.1	1003	1138.6
Yes[1]	1026	1126.5	1014	1135.1

[1] Diabetes mellitus status at baseline comprised T2DM patients only; there were no T1DM patients.

Data source: data on file, SAF-HF5(HFrEF), Table 3.1.1.7

SIII.4 ADULT T2DM INDICATION

SAF-43 comprised cumulative data of 4904 patients receiving placebo and 10 177 patients receiving empagliflozin of which 4858 patients were treated with 10 mg empagliflozin only, 5057 patients with empagliflozin 25 mg only, and 162 patients with dose escalation of empagliflozin of 10 mg to 25 mg. More than half of the patients in each treatment group were exposed for up to 75 weeks to trial medication. The total cumulative patient-time was higher in the empagliflozin treatment groups than for placebo. An overview of cumulative exposure is given in SIII.Table 15.

All treatment groups comprised fewer female than male patients. The largest proportion of patients was younger than 65 years in both the male and female groups with a comparable distribution across age categories within the respective male and female groups. Further details are given in SIII.Table 16.

With regard to ethnic origin (i.e. race), the largest proportion of patients in all treatment groups was White, followed by Asian. A tabular overview is given in SIII.Table 17.

SIII.Table 15 Duration of exposure (SAF-43) - TS

	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg		Empagliflozin 10/25 mg[1]	
	Patients N (%)	Person-time [PY]	Patients N (%)	Person-time [PY]	Patients N (%)	Person-time [PY]	Patients N (%)	Person-time [PY]
Cumulative exposure								
≥0 weeks	4904 (100.0)	7857.1	4858 (100.0)	8044.0	5057 (100.0)	8225.7	10 177 (100.0)	16479.8
≥4 weeks	4838 (98.7)	7855.0	4794 (98.7)	8042.3	4980 (98.5)	8222.9	10 031 (98.6)	16475.1
≥8 weeks	4693 (95.7)	7840.6	4665 (96.0)	8029.9	4842 (95.7)	8209.4	9758 (95.9)	16448.7
≥14 weeks	4089 (83.4)	7701.8	4086 (84.1)	7896.5	4244 (83.9)	8071.8	8578 (84.3)	16177.0
≥20 weeks	3902 (79.6)	7642.9	3625 (74.6)	7752.7	3767 (74.5)	7923.6	7637 (75.0)	15884.2
≥26 weeks	3503 (71.4)	7457.9	3328 (68.5)	7614.9	3469 (68.6)	7785.2	6976 (68.5)	15577.3
≥49 weeks	3289 (67.1)	7313.1	3173 (65.3)	7509.4	3332 (65.9)	7692.6	6677 (65.6)	15374.1
≥60 weeks	2624 (53.5)	6644.7	2793 (57.5)	7127.8	2746 (54.3)	7104.2	5539 (54.4)	14232.0
≥75 weeks	2512 (51.2)	6501.0	2714 (55.9)	7027.5	2673 (52.9)	7010.5	5387 (52.9)	14037.9
≥100 weeks	1943 (39.6)	5545.8	2099 (43.2)	5996.4	2096 (41.4)	6040.4	4195 (41.2)	12036.9
≥126 weeks	1197 (24.4)	3952.2	1284 (26.4)	4259.0	1301 (25.7)	4345.6	2585 (25.4)	8604.6
≥152 weeks	918 (18.7)	3195.8	977 (20.1)	3425.5	1008 (19.9)	3550.5	1985 (19.5)	6976.0
≥178 weeks	528 (10.8)	1943.9	597 (12.3)	2203.6	623 (12.3)	2310.1	1220 (12.0)	4513.7
≥204 weeks	124 (2.5)	492.4	136 (2.8)	541.1	171 (3.4)	682.3	307 (3.0)	1223.4

[1] Contains empagliflozin 10 mg, empagliflozin 25 mg as well as empagliflozin 10 mg/25 mg of trials 1245-0029 (dose escalation) and 127-00.19 (up-titration).
Data source: data on file, SAF-43, Table 31.3.1.1

SIII.Table 16 Age group and gender (SAF-43) - TS

Gender/ Age group [years]	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg		Empagliflozin 10/25 mg[1]	
	Patients N	Person-time [PY]	Patients N	Person-time [PY]	Patients N	Person-time [PY]	Patients N	Person-time [PY]
Male								
<65	2007	3286.9	2001	3354.5	2098	3464.8	4228	6923.2
65 to <75	885	1588.7	914	1753.3	947	1841.4	1910	3639.2
75 to <85	220	427.1	173	326.2	195	368.2	376	702.4
≥85	7	16.9	6	8.2	9	19.7	15	27.9
Female								
<65	1190	1581.1	1167	1611.1	1195	1595.8	2411	3239.1
65 to <75	492	790.3	476	766.5	479	743.1	977	1526.2
75 to <85	98	160.5	117	221.3	132	189.3	254	415.7
≥85	5	5.7	4	2.9	2	3.4	6	6.2

[1] Contains empagliflozin 10 mg, empagliflozin 25 mg as well as empagliflozin 10 mg/25 mg of trials 1245-0029 (dose escalation) and 1275-0019 (up-titration).
Data source: data on file, SAF-43, Table 31.3.1.4

SIII.Table 17 Ethnic origin (SAF-43) – TS

Race	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg		Empagliflozin 10/25 mg[1]	
	Patients N	Person-time [PY]	Patients N	Person-time [PY]	Patients N	Person-time [PY]	Patients N	Person-time [PY]
White	3044	5095.6	3256	5363.7	3346	5502.3	6602	10866.0
Black	279	377.8	213	352.9	219	347.8	512	733.7
Asian	1347	2146.0	1252	2186.3	1349	2205.9	2601	4392.2
Native Hawaiian/other Pacific Islander	12	13.6	8	12.5	7	8.1	15	20.6
American Indian/Alaska Native	39	54.4	42	46.5	44	71.7	86	118.2

[1] Contains empagliflozin 10 mg, empagliflozin 25 mg as well as empagliflozin 10 mg/25 mg of trials 1245-0029 (dose escalation) and 1275-0019 (up-titration).

Data source: data on file, SAF-43, Table 31.3.1.5

SIII.5 POOLED INDICATIONS

Indications CKD+HF+adult and paediatric T2DM

Pooling CKD+HF+T2DM+PAED comprised cumulative data of 13 577 patients receiving placebo and 18 921 patients empagliflozin. About half of the patients in either treatment group were exposed for up to 78 weeks to trial medication. The total cumulative patient-time was higher in the empagliflozin treatment group than for placebo. An overview of cumulative exposure is given in SIII.Table 18.

Both treatment groups comprised fewer female than male patients. The largest proportion of patients was younger than 65 years in both the male and female groups with a comparable distribution across age categories within the respective male and female groups. Further details are given in SIII.Table 19.

With regard to ethnic origin, the largest proportion of patients in both treatment groups was White, followed by Asian. A tabular overview is given in SIII.Table 20.

SIII.Table 18 Duration of exposure (pooling CKD+HF+T2DM+PAED) - TS

	Placebo		All Empa[1]	
	Patients N (%)	Person-time [PY]	Patients N (%)	Person-time [PY]
Cumulative exposure				
≥0 weeks	13 577 (100.0)	21 626.2	18 921 (100.0)	30 344.4
≥12 weeks	12 740 (93.8)	21 525.4	17 801 (94.1)	30 210.9
≥26 weeks	10 829 (79.8)	20 909.8	14 344 (75.8)	29 099.7
≥52 weeks	9677 (71.3)	20 065.1	13 008 (68.7)	28 100.8
≥78 weeks	7143 (52.6)	16 920.8	9900 (52.3)	24 304.7
≥104 weeks	4832 (35.6)	12 918.8	6892 (36.4)	19 056.8
≥156 weeks	1242 (9.1)	4235.6	2299 (12.2)	7989.4

[1] All Empa contains empagliflozin 10 mg, empagliflozin 25 mg as well as empagliflozin 10 mg/25 mg of trials 1218-0091, 1245-0029 (dose escalation), and 1275-0019 (up-titration).

Data source: data on file, x1245csap54-060601-study-report-body-final, Table 6.1.1

SIII.Table 19 Age group and gender (pooling CKD+HF+T2DM+PAED) - TS

Gender/ Age group [years]	Placebo		All Empa[1]	
	Patients N	Person-time [PY]	Patients N	Person-time [PY]
Male				
<65	4038	6458.2	6238	10 077.2
65 to <75	2804	4702.9	3910	6775.2
≥75	1875	2986.1	2048	3309.3
Female				
<65	2166	3148.5	3363	4745.9
65 to <75	1483	2415.8	2016	3256.1
≥75	1211	1914.8	1346	2180.8

[1] All Empa contains empagliflozin 10 mg, empagliflozin 25 mg as well as empagliflozin 10 mg/25 mg of trials 1218-0091, 1245-0029 (dose escalation), and 1275-0019 (up-titration).

Data source: data on file, x1245csap54-060601-study-report-body-final, Table 6.1.7

SIII.Table 20 Ethnic origin (pooling CKD+HF+T2DM+PAED) – TS

Race	Placebo		All Empa[1]	
	Patients N	Person-time [PY]	Patients N	Person-time [PY]
American Indian/Alaska Native	172	279.2	196	310.6
Asian	3486	5684.7	4993	8133.8
Black/African American	757	996.7	967	1380.4
Native Hawaiian/Pacific Islander	37	54.5	36	60.1
White	8927	14 310.7	12 561	20 215.1
Multiple	118	186.4	107	153.6

[1] All Empa contains empagliflozin 10 mg, empagliflozin 25 mg as well as empagliflozin 10 mg/25 mg of trials 1218-0091, 1245-0029 (dose escalation), and 1275-0019 (up-titration).

Data source: data on file, x1245csap54-060601-study-report-body-final, Table 6.1.11

SIII.6 REFERENCES

SIII.6.1 Published references

Not applicable.

SIII.6.2 Unpublished references

c37800399-01 A multicentre international randomized parallel group double-blind placebo-controlled clinical trial of EMPAgliflozin once daily to assess

cardio-renal outcomes in patients with chronic KIDNEY disease. 1245-0137. 28 Oct 2022

ABBREVIATIONS

CKD	Chronic kidney disease
CTR	Clinical trial report
DINAMO	Study acronym; DIabetes study of liNAgliptin and eMpagliflozin in children and adOlescents
Empa	Empagliflozin
EMPA-KIDNEY	Study acronym; The Study of Heart and Kidney Protection With Empagliflozin)
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
PY	Patient-years
RMP	Risk management plan
RS	Randomised set
SAF	Safety analysis set
SD	Standard deviation
T2DM	Type 2 diabetes mellitus
TS	Treated set

MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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

All indications

Hypersensitivity to the active substance or to any of the excipients

Reason for exclusion:	Patients with known hypersensitivity reactions to the active substance or to any of the excipients are excluded from clinical trials for safety reasons, to safeguard the wellbeing of susceptible patients.
Is it considered to be included as missing information?	No
Rationale:	Known hypersensitivity cannot be considered as missing information. Hypersensitivity to the active substance or to any of the excipients is covered in the SmPC as contraindication.

Pregnancy/breast-feeding

Reason for exclusion:	Clinical trials in pregnant or nursing women cannot be conducted for ethical reasons.
Is it considered to be included as missing information?	No
Rationale:	Very limited experience is available from clinical trial and post-marketing data. The risk for the unborn or breastfed child is not known, but cannot be excluded. Therefore, this topic is considered missing information.

Liver disease (defined as an increase in liver enzymes)

Reason for exclusion:	To detect liver disorders during treatment with empagliflozin.
Is it considered to be included as missing information?	No
Rationale:	Pharmacokinetic data did not show a clinically relevant increase in exposure of empagliflozin in patients with liver disease. Based on all safety data obtained so far, no new safety concern is expected in this population.

Elderly patients (≥85 years)

Reason for exclusion:	Elderly patients per se are not excluded from participation in clinical trials; however, clinical trial exposure in elderly patients is limited.
Is it considered to be included as missing information?	No
Rationale:	Patients ≥75 years are at an increased risk of volume depletion; the risk of volume depletion in patients ≥85 years is not known but might be increased. Based on all safety data obtained so far, no new safety concern is expected in this population.

Adult T2DM indication

Uncontrolled hyperglycaemia with HbA_{1c} >10%

Reason for exclusion:	Empagliflozin was investigated in a placebo-controlled trial design. For ethical reasons, patients with uncontrolled hyperglycaemia were not included.
Is it considered to be included as missing information?	No
Rationale:	Open-label treatment of patients with high HbA_{1c} (>10%) showed efficacy in patients with severe hyperglycaemia. Although the safety profile of empagliflozin is not expected to be different in patients with uncontrolled hyperglycaemia with an HbA_{1c} >10%, this poorly controlled patient population was excluded in the phase III trials. This patient population may also be at a greater risk of experiencing the acute complications of T2DM treatment (e.g. severe hypoglycaemia and DKA) and as such this population was also excluded for safety reasons.

Blood dyscrasia

Reason for exclusion:	To be able to measure HbA_{1c} in patients with haemoglobinopathies and to safeguard the assessment and readout of the primary endpoint of the trials (HbA_{1c}).
Is it considered to be included as missing information?	No
Rationale:	The safety profile of empagliflozin is not expected to be different in patients with blood dyscrasia.

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 primary endpoints of the trials. Therefore, to minimise any confounders for interpreting the efficacy impact of empagliflozin in patients with T2DM, treatment with systemic steroids was an exclusion criterion.
Is it considered to be included as missing information?	No
Rationale:	The safety profile of empagliflozin is not expected to be different in patients treated with systemic steroids.

Bariatric surgery within 2 years

Reason for exclusion:	To assess a possible weight effect of empagliflozin treatment and to minimise any confounders for interpreting the effects of empagliflozin on weight changes in patients with T2DM.
Is it considered to be included as missing information?	No
Rationale:	The safety profile of empagliflozin is not expected to be different in patients with bariatric surgery.

Treatment with anti-obesity drugs

Reason for exclusion:	To assess a possible weight effect of empagliflozin treatment and to minimise any confounders for interpreting the effects of empagliflozin on weight changes in patients with T2DM.
Is it considered to be included as missing information?	No
Rationale:	The safety profile of empagliflozin is not expected to be different in patients treated with anti-obesity drugs.

BMI ≥45 kg/m^2

Reason for exclusion:	To assess a possible weight effect of empagliflozin treatment and to minimise any confounders for interpreting efficacy results by minimising potential insulin resistance effects.
Is it considered to be included as missing information?	No
Rationale:	The safety profile of empagliflozin is not expected to be different in patients with a BMI ≥45 kg/m^2.

Renal impairment

Reason for exclusion:	Due to the mechanism of action, the glycaemic efficacy of empagliflozin is dependent on renal function. Patients with severe renal impairment (eGFR <30 mL/min/1.73m^2, using the MDRD formula) were to be excluded from most clinical trials.
Is it considered to be included as missing information?	No
Rationale:	A dedicated clinical trial (1245-0036) in patients with T2DM and severe renal impairment (eGFR <30 mL/min/1.73m^2) showed the safety use of empagliflozin in this patient population up to 1 year of treatment. Although the safety profile of empagliflozin is not different in patients with severe renal impairment, empagliflozin should not be used in patients with end-stage renal disease or in patients with dialysis as it is not expected to be effective in these patients.

Children less than 10 years old

Reason for exclusion:	A paediatric waiver is in place for children under 10 years old.
Is it considered to be included as missing information?	No
Rationale:	The disease does not occur in this paediatric subset.

Indication heart failure

Renal impairment

Reason for exclusion:	Due to the presumed mechanism of action, it is considered likely that the efficacy of empagliflozin may be dependent on renal function. Patients with severe renal impairment (EMPEROR trials, eGFR <20 mL/min/1.73m^2) were to be excluded.
Is it considered to be included as missing information?	No
Rationale:	AEs by baseline eGFR were generally consistent with the AE profile in the overall population (EMPEROR trials). Although the safety profile of empagliflozin is not different in patients with severe renal impairment, it is not recommended to use empagliflozin in patients with end-stage renal disease or in patients with dialysis as it is not known if it may be effective in these patients.

Paediatric patients

Reason for exclusion:	A paediatric waiver is in place for the HF clinical programme.
Is it considered to be included as missing information?	No
Rationale:	Benefit-risk for paediatric patients is not established. A paediatric waiver is in place for the HF clinical programme.

Indication CKD

T2DM and prior atherosclerotic cardiovascular disease with an eGFR >60 mL/min/1.73m^2 at screening

Reason for exclusion:	Patients with T2DM and prior CVD and an eGFR>60 mL/min/1.73m^2 have been extensively studied in the EMPA-REG OUTCOME trial, therefore it was decided to generate clinical evidence of efficacy and safety in CKD patients with clinical characteristics other than the EMPA-REG OUTCOME population.
Is it considered to be included as missing information?	No
Rationale:	The safety and efficacy of empagliflozin has already been evaluated in the EMPA-REG OUTCOME trial.

Patients on dialysis/renal impairment

Reason for exclusion:	Empagliflozin 10 mg can be used regardless of renal function. However, due to limited experience, it is not

	recommended to initiate treatment with empagliflozin in patients on dialysis.
Is it considered to be included as missing information?	No
Rationale:	AEs by baseline eGFR were generally consistent with the AE profile in the overall population (EMPA-KIDNEY).

Patients with a functioning kidney transplant or scheduled for a living donor transplant

Reason for exclusion:	Patients with a functioning transplant receive immunosuppressive treatment and are generally at a higher risk of infection. Although empagliflozin is generally well tolerated with regards to infections (except for an increase of genital mycotic infections), it is unclear whether it is safe to use empagliflozin in transplant patients.
Is it considered to be included as missing information?	No
Rationale:	Although smaller retrospective and prospective studies did not identify a higher risk of infection with empagliflozin in transplant patients, still it is currently unclear whether the use of empagliflozin is safe in these patients given the limited body of evidence.

Patients with polycystic kidney disease

Reason for exclusion:	Based on the empagliflozin's suspected mode of action, the compound is not expected to be effective in patient with polycystic kidney disease.
Is it considered to be included as missing information?	No
Rationale:	The safety profile of empagliflozin is not expected to be different in patients with polycystic kidney disease. Despite these safety considerations, based on the mode of action empagliflozin is not expected to be effective in this patient population.

Previous or scheduled bariatric surgery

Reason for exclusion:	Patients with previous or scheduled bariatric surgery appear to have an increased risk for hypoglycaemia and ketoacidosis due to potentially fast decline in body weight and alteration of dietary habits.
Is it considered to be included as missing information?	No
Rationale:	The safety profile of empagliflozin is not expected to be

	different in patients with previous or scheduled bariatric surgery.

Any intravenous immunosuppression therapy in last 3 months; or anyone currently on >45 mg prednisolone (or equivalent)

Reason for exclusion:	CKD patients on intensified immunosuppressive treatment are generally at a higher risk of infection. Although empagliflozin is generally well tolerated with regards to infections (except for an increase of genital mycotic infections), it is unclear whether it is safe to use empagliflozin in CKD patients on intensified immunosuppressive regimens. Furthermore, as intensive immunosuppression can be a confounding factor in the assessment of kidney protective effects of empagliflozin, and thus interfere with the primary/secondary endpoints of the trials.
Is it considered to be included as missing information?	No
Rationale:	Although efficacy can be expected to be comparable in CKD patients on immunosuppressive treatment and the general CKD population, it is unclear whether it is safe to use empagliflozin in CKD patients on intensified immunosuppressive regimens.

T1DM

Reason for exclusion:	Exclusion of CKD patients with T1DM was added via a protocol amendment as too few patients were expected to provide sufficiently robust efficacy and safety data for this population.
Is it considered to be included as missing information?	No
Rationale:	Limited evidence in CKD patients would have been generated.

<u>Paediatric T2DM indication</u>

Uncontrolled hyperglycaemia with HbA_{1c} >10.5%

Reason for exclusion:	For ethical reasons, patients with uncontrolled hyperglycaemia of HbA_{1c} >10.5% were not included.
Is it considered to be included as missing information?	No
Rationale:	Open-label treatment of patients with high HbA_{1c} (>10%) showed efficacy in patients with severe hyperglycaemia. Although the safety profile of empagliflozin is not

	expected to be different in children and adolescence with uncontrolled hyperglycaemia with an HbA_{1c} >10.5%, this poorly controlled patient population was excluded. This patient population may also be at a greater risk of experiencing the acute complications of T2DM treatment (e.g. severe hypoglycaemia and DKA) and as such this population was also excluded for safety reasons.

Treatment with systemic corticosteroids for >1 week

Reason for exclusion:	Prolonged treatment with systemic steroids can be a confounding factor in the assessment of body weight and glucose lowering, and thus interfere with the primary endpoints of the trials. Therefore, to minimise any confounders for interpreting the efficacy impact of empagliflozin in children and adolescence with T2DM, treatment with systemic steroids for >than 1 week was an exclusion criterion.
Is it considered to be included as missing information?	No
Rationale:	The safety profile of empagliflozin is not expected to be different in children and adolescence treated with systemic steroids for >1 week.

Impaired renal function eGFR <60 mL/min/1.73m² (using Zappitelli formula)

Reason for exclusion:	Due to the mechanism of action, the glycaemic efficacy of empagliflozin is dependent on renal function. T2DM children and adolescence with renal impairment (eGFR <60 mL/min/1.73m^2, using Zappitelli formula) were excluded.
Is it considered to be included as missing information?	No
Rationale:	AEs by baseline eGFR were generally consistent with the AE profile in the overall population. Although the safety profile of empagliflozin is not different in patients with renal impairment, it is not recommended to use empagliflozin in T2DM children and adolescence with renal disease in this patient population.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

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

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

Type of special population	Exposure			
Pregnant women	Clinical development programme: n = 12 Post-authorisation data: n = 57			
Breast-feeding women	Not included in the clinical development programme.			
Patients with relevant co-morbidities	Placebo (Number/person-time [PY])		All Empa (Number/person-time [PY])	
• Patients with hepatic impairment (pooling CKD+HF+T2DM+PAED)				
○ Hepatic impairment - no	13 569	21 615.4	18 914	30 339.2
○ Hepatic impairment - yes	8	10.8	7	5.2
• Patients with renal impairment (pooling CKD+HF+T2DM+PAED)[1]				
○ <30 (CKD-EPI)/<60 (Zappitelli)	1453	2402.0	1473	2484.9
○ 30 to <45 (CKD-EPI)/ 60 to <90 (Zappitelli)	2697	4548.4	2881	4904.3
○ 45 to <60 (CKD-EPI)/ 90 to <120 (Zappitelli)	2302	3809.6	2778	4812.9
○ 60 to <90 (CKD-EPI)/ 120 to <150 (Zappitelli)	4624	7470.1	6999	11 681.3
○ ≥90 (CKD-EPI)/ ≥150 (Zappitelli)	2484	3390.0	4774	6456.5
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme.			
Population with relevant different ethnic origin	See Module SIII for information on ethnic origin.			
Subpopulations carrying relevant genetic polymorphisms	Samples from a metabolically well phenotyped cross-sectional study population (n = 2600) at increased risk for T2DM and pooled pharmacogenetic samples from patients from 4 phase III trials of empagliflozin (603 receiving empagliflozin, 305 receiving placebo) were genotyped for 5 common SNPs (minor allele frequencies ≥5%) present in the SLC5A2 gene locus [P17-01242].			
Other	Not included in the clinical development programme.			

[1] eGFR (mL/min/1.73m^2) at baseline using the CKD-EPI formula (<30, 30 to <45, 45 to <60, 60 to <90, ≥90) or Zappitelli (<60, 60 to <90, 90 to <120, 120 to <150, ≥150)

Data source: data on file, x1245csap54-060601-study-report-body-final, Tables 6.1.13, 6.1.15; and BI GSP

SIV.4 REFERENCES

SIV.4.1 Published references

P17-01242 Zimdahl H, Haupt A, Brendel M, Bour L, Machicao F, Salsali A, et al. Influence of common polymorphisms in the SLC5A2 gene on metabolic traits in subjects at increased risk of diabetes and on response to empagliflozin treatment in patients with diabetes. Pharmacogenetics and Genomics, Post Author Corrections: January 27, 2017, doi: 10.1097/FPC.0000000000000268 Pharmacogenet Genomics 2017. 27(4):135-142

SIV.4.2 Unpublished references

Not applicable.

ABBREVIATIONS

AE	Adverse event
BMI	Body mass index
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVD	Cardiovascular disease
DKA	Diabetic ketoacidosis
eGFR	Estimated glomerular filtration rate
Empa	Empagliflozin
EASE	Study acronym; Empagliflozin as Adjunctive to inSulin thErapy in
EMPA-KIDNEY	Study acronym; The Study of Heart and Kidney Protection With Empagliflozin)
EMPA-REG OUTCOME	Study acronym; EMPAgliflozin Removal of Excess of Glucose OUTCOME trial
EMPEROR	Study acronym; EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure
HbA_{1c}	Glycated haemoglobin
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
MDRD	Modification of Diet in Renal Disease
PY	Patient-years

SmPC	Summary of Product Characteristics
SNP	Single nucleotide polymorphisms
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

SV.1.1 Method used to calculate exposure

The method used to estimate patient exposure to the marketed drug is based on the number of tablets sold (ex-factory sales). It was assumed that all tablets were used by the patients. Assuming further that each patient was treated with 1 tablet per day (defined daily dose), and was treated for 365.25 days as the therapy duration. The total number of days of medication is then divided by 365.25 to calculate the total patient exposure in PY.

SV.1.2 Exposure

Calculated cumulative exposure figures are presented by dose and region in the table below. As there is only 1 formulation (tablet) for Jardiance, a presentation by this variable is not applicable. The overall cumulative patient exposure to marketed Jardiance is estimated to be 15 319 021 PY for the period April 2014 to April 2021. Marketing experience in the heart failure indication is not yet available.

SV.Table 1 Cumulative exposure from marketing experience by dose and region for Jardiance (April 2014 to April 2021) - T2DM indication

Region/ Dose	Cumulative exposure [PY]				Total
	[redacted]				
Tablet, 10 mg	[redacted]	[redacted]	[redacted]	[redacted]	8 248 029
Tablet, 25 mg	[redacted]	[redacted]	[redacted]	[redacted]	7 070 992
Total	[redacted]	[redacted]	[redacted]	[redacted]	**15 319 021**

Note: All numbers are rounded to the nearest integer

Data source: Jardiance/Synjardy PBRER, reporting interval 18 Apr 2019 to 17 Apr 2021 [s00096926-01]. Table 7

SV.Table 2 Cumulative exposure from marketing experience by dose and EU/EEA country for Jardiance (April 2014 to April 2021) - T2DM indication

EU/EEA country	Cumulative exposure [PY]	
	Tablet, 10 mg	Tablet, 25 mg
[redacted]		

Note: All numbers are rounded to the nearest integer.
Data source: data on file, EA-003 Jardiance exposure (2021 04)

SV.2 REFERENCES

SV.2.1 Published references

Not applicable.

SV.2.2 Unpublished references

s00096926-01 Periodic Benefit-Risk Evaluation Report for Jardiance (empagliflozin) and Synjardy (empagliflozin + metformin), reporting interval 18 Apr 2019 to 17 Apr 2021. 04 Jun 2021

ABBREVIATIONS

EEA	European Economic Area
EU	European Union
PY	Patient-years
T2DM	Type 2 diabetes mellitus
US	United States

MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Empagliflozin is available as prescription medicine only. 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; or other effects that might lead to dependency. Abuse for illegal purpose is not expected with empagliflozin.

SVI.2 REFERENCES

Not applicable.

ABBREVIATIONS

EU	European Union

MODULE SVII IDENTIFIED AND POTENTIAL RISKS

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

Since this is not an initial RMP submission, only an overview of the safety concerns identified at the time of first authorisation is provided below.

SVII.Table 1 Summary of safety concerns at the time of first marketing authorisation

Important identified risks	Urinary tract infection
	Genital infection
	Volume depletion
	Hypoglycaemia (with insulin and/or SU)
Important potential risks	Urinary tract carcinogenicity
	Renal impairment
	Liver injury
	Off-label use (e.g. for weight loss in non-T2DM patients)
	Bone fracture
Missing information	Paediatric patients
	Elderly patients
	Pregnancy/breast-feeding
	Clinical impact of dyslipidaemia
	Long-term safety (particularly cardiovascular)
	Concomitant use with GLP-1 analogues
	Use in patients with severe hepatic impairment
	Missing long-term safety information on melanoma

Data source: Jardiance EU-RMP v1.4 [s00017688-06], SVIII.Table 1

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

SVII.2.1 Changes in the safety concerns from v19.0

As an outcome of the Article 20 referral on the risk of lower limb amputation in the EU, BI was requested to conduct a meta-analysis of the 2 chronic heart failure trials (1245-0110 and 1245-0121) together with the EMPA-REG OUTCOME trial (1245-0025) as additional pharmacovigilance activity (PASS 1245-0171). The milestone of PASS 1245-0171 (final

report) was completed (EMEA/H/C/002677/WS/2196); results of the meta-analysis are summarised below.

In addition, EMPA-KIDNEY (1245-0137) was categorised as a PASS to investigate the risk for the occurrence of LLA with empagliflozin. The milestone of this PASS was completed. A post-hoc meta-analysis was performed, including 4 large, randomised, double-blind, placebo-controlled clinical trials: EMPA-KIDNEY (1245-0137), EMPA-REG OUTCOME (1245-0025), EMPEROR-Preserved (1245-0110), and EMPEROR-Reduced (1245-0121). Results of the post-hoc meta-analysis are summarised below.

Both meta-analyses did not show an increased risk of LLA for patients treated with empagliflozin. Based on the results of the 2 meta-analyses and in line with GVP Module V Rev 2 recommendations, 'Amputation risk' is proposed to be removed from the list of safety concerns from the EU-RMP. The topic will continue to be monitored in the PBRER.

SVII.2.1.1 PASS 1245-0171 [c32096554-01]

Objectives

The primary objective of this exploratory meta-analysis was to evaluate the frequencies, IRs, and HRs of LLA events (primary outcome) and of AEs related to amputation (secondary outcome) in patients treated with empagliflozin compared with placebo in the pooled population of the long-term trials 1245-0025, 1245-0110, and 1245-0121 (SAF-M1), in the pooled population of trials 1245-0110 and 1245-0121 (SAF-M2), and in each of the 3 trials separately.

The exploratory objectives were to evaluate the frequencies of recurrent LLA events and of AEs related to recurrent LLA events and to assess the frequencies and IRs of patients with AEs related to amputation preceding the amputation for empagliflozin compared with placebo in SAF-M1, SAF-M2, and in each of the 3 trials separately. Further exploratory objectives were to evaluate the frequencies, IRs, and HRs of the primary and secondary outcomes by subgroup and of the secondary outcome by grouped PTs for SAF-M1 and SAF-M2 as well as to assess details on LLA events for SAF-M2 in patients treated with empagliflozin compared with placebo.

Study design

This meta-analysis included 3 randomised, placebo-controlled, double-blind, parallel-group, and event-driven trials, each of which has recruited an overlapping but unique patient population (trials 1245-0025, 1245-0110, and 1245-0121). The 1245-0025 trial was conducted in patients with T2DM and established CV disease, and included 2 dose groups treated with empagliflozin compared with placebo. The trials 1245-0110 and 1245-0121 were conducted in patients with HF (HFpEF and HFrEF, respectively, with or without T2DM) and included only 1 dose group of empagliflozin (10 mg) vs. placebo. Consequently, in SAF-M1, the pooled empagliflozin arm includes about twice as many patients from trial 1245-0025 compared to the pooled placebo arm, resulting in differences in sample size and composition between the 2 treatment arms (see SVII.Table 2 for number of patients receiving placebo and empagliflozin in SAF-M1 and SAF-M2).

Due to this study design effect, the pooled SAF-M1 frequencies and IRs should not directly be compared between placebo and empagliflozin. Rather, the HRs should be used to interpret SAF-M1 results. In contrast, SAF-M2 is limited to the 2 HF trials, and includes a similar proportion of patients from each trial in each treatment group.

Results

Primary outcome

In general, the frequencies of LLAs were low and similar for both the empagliflozin and placebo treatment groups (see a summary by analysis population and trial in SVII.Table 2 below). Most patients with LLAs had only a single episode of LLA (SAF-M1: empagliflozin: 68/95 patients with LLAs; placebo: 46/55 patients with LLAs).

In the analysis of the primary outcome (LLAs), in both the SAF-M1 and SAF-M2 populations, the results did not indicate an increased risk of LLAs in patients treated with empagliflozin. The findings in the individual trials were consistent with those from the overall populations of SAF-M1 and SAF-M2. A summary of patients with LLAs on treatment, IRs for LLAs on treatment, and HRs for empagliflozin vs. placebo is tabulated below for the primary outcome in SAF-M1, SAF-M2, and the individual trials. Adjusting for death as a competing risk, in SAF-M1 the HR for LLAs for empagliflozin vs. placebo was almost unchanged from the primary analysis: HR=1.02 (95% CI 0.73, 1.43; p=0.9017). There were also no clinically meaningful differences in findings when the analyses were conducted on an ITT basis, including LLAs to the last follow-up. In the ITT analysis of the SAF-M1 population the HR for LLAs for empagliflozin vs. placebo was almost unchanged from the primary analysis: HR=0.96 (95% CI 0.72, 1.29; p=0.7985). For SAF-M2, the HR was 0.89 (95% CI 0.54, 1.46; p=0.6314) (PASS 1245-0171 [c32096554-01], Section 1).

Considering the potential differences in patient populations, subgroup analyses by demographics, baseline medical conditions, and baseline therapies were carried out to assess any potential impact of these differences on the results. In subgroup analyses, there were no patterns identified to suggest a substantial impact of empagliflozin on risk of LLAs, also including in subgroups of patients with a higher risk of LLA.

SVII.Table 2 Summary of primary outcome analyses; Cox regression for time to first LLA – on treatment (by analysis population/individual trial)

Population/trial	Placebo	Empagliflozin
SAF-M1		
Number of patients analysed, N	7185	9546
Patients with LLA events, N (%)	55 (0.8)	95 (1.0)
Incidence rate[1] (95% CI)	0.40 (0.30, 0.52)	0.48 (0.39, 0.58)
HR (95% CI); p value[2]	1.02 (0.73, 1.42); 0.9276	
SAF-M2		
Number of patients analysed, N	4852	4859
Patients with LLA events, N (%)	21 (0.4)	18 (0.4)
Incidence rate[1] (95% CI)	0.27 (0.17, 0.39)	0.23 (0.13, 0.34)
HR (95% CI); p value[2]	0.85 (0.45, 1.60); 0.6205	
1245-0025		
Number of patients analysed, N	2333	4687
Patients with LLA events, N (%)	34 (1.5)	77 (1.6)
Incidence rate[1] (95% CI)	0.59 (0.41, 0.81)	0.64 (0.51, 0.79)
HR (95% CI); p value[2]	1.09 (0.73, 1.63); 0.6768	
1245-0110		
Number of patients analysed, N	2989	2996
Patients with LLA events, N (%)	15 (0.5)	11 (0.4)
Incidence rate[1] (95% CI)	0.27 (0.15, 0.42)	0.20 (0.10, 0.33)
HR (95% CI); p value[2]	0.73 (0.34, 1.59); 0.4294	
1245-0121		
Number of patients analysed, N	1863	1863
Patients with LLA events, N (%)	6 (0.3)	7 (0.4)
Incidence rate[1] (95% CI)	0.27 (0.10, 0.52)	0.31 (0.12, 0.58)
HR (95% CI); p value[2]	1.17 (0.39, 3.47); 0.7826	

[1] Patients with events per 100 PY

[2] Based on a Cox regression model with terms for trial (for SAF-M1 and SAF-M2 only), baseline diabetes status (not for 1245-0025), and treatment.

Data source: PASS 1245-0171 [c32096554-01], Section 1, Table 1

Secondary outcomes

A summary of frequencies of vascular disorders, diabetic-foot-related events, infections potentially related to LLAs, wound/infections, nervous system disorders, and volume depletion events prior to an LLA, incidence rates, HRs (95%) CIs, and p-values for these AEs are provided below (SVII.Table 3 and SVII.Table 4 for SAF-M1 and SAF-M2, respectively).

In the subgroup analyses, there were no patterns identified to suggest a substantial impact of empagliflozin on risk of the secondary outcomes in subgroups of patients compared with the overall population.

SVII.Table 3 Summary of secondary outcome analyses – AEs potentially related to LLAs (occurring before an LLA) – SAF-M1 - on treatment

AEs	Placebo	Empagliflozin
Number of patients analysed, N	7185	9546
Vascular AEs		
Patients with LLA events, N (%)	198 (2.8)	306 (3.2)
Incidence rate[1] (95% CI)	1.48 (1.28, 1.69)	1.57 (1.40, 1.75)
HR (95% CI); p value[2]	1.00 (0.83, 1.20); 0.9946	
Diabetic-foot-related AEs		
Patients with LLA events, N (%)	68 (0.9)	127 (1.3)
Incidence rate[1] (95% CI)	0.50 (0.39, 0.63)	0.64 (0.53, 0.76)
HR (95% CI); p value[2]	1.15 (0.85, 1.55); 0.3612	
Infections potentially related to LLAs		
Patients with LLA events, N (%)	290 (4.0)	396 (4.1)
Incidence rate[1] (95% CI)	2.19 (1.94, 2.44)	2.04 (1.85, 2.25)
HR (95% CI); p value[2]	0.89 (0.77, 1.04); 0.1526	
Wound infections		
Patients with LLA events, N (%)	115 (1.6)	168 (1.8)
Incidence rate[1] (95% CI)	0.86 (0.71, 1.02)	0.86 (0.73, 0.99)
HR (95% CI); p value[2]	0.89 (0.70, 1.13); 0.3396	
Nervous system disorders		
Patients with LLA events, N (%)	205 (2.9)	349 (3.7)
Incidence rate[1] (95% CI)	1.54 (1.34, 1.76)	1.81 (1.62, 2.00)
HR (95% CI); p value[2]	1.00 (0.84, 1.19); 0.9992	
Volume depletion		
Patients with LLA events, N (%)	90 (1.3)	129 (1.4)
Incidence rate[1] (95% CI)	0.67 (0.54, 0.81)	0.65 (0.54, 0.77)
HR (95% CI); p value[2]	1.21 (0.92, 1.58); 0.1765	

1 Patients with events per 100 PY

2 Based on a Cox regression model with terms for trial, baseline diabetes status, and treatment.

Data source: PASS 1245-0171 [c32096554-01], Section 1, Table 2

SVII.Table 4 Summary of secondary outcome analyses – AEs potentially related to LLAs (occurring before an LLA) – SAF-M2 - on treatment

AEs	Placebo	Empagliflozin
Number of patients analysed, N	4852	4859
Vascular AEs		
Patients with LLA events, N (%)	99 (2.0)	95 (2.0)
Incidence rate[1] (95% CI)	1.27 (1.03, 1.54)	1.21 (0.98, 1.47)
HR (95% CI); p value[2]	0.95 (0.72, 1.27); 0.7474	
Diabetic-foot-related AEs		
Patients with LLA events, N (%)	25 (0.5)	36 (0.7)
Incidence rate[1] (95% CI)	0.32 (0.21, 0.46)	0.46 (0.32, 0.62)
HR (95% CI); p value[2]	1.44 (0.86, 2.40); 0.1610	
Infections potentially related to LLAs		
Patients with LLA events, N (%)	143 (2.9)	139 (2.9)
Incidence rate[1] (95% CI)	1.85 (1.56, 2.17)	1.78 (1.50, 2.09)
HR (95% CI); p value[2]	0.96 (0.76, 1.21); 0.7430	
Wound infections		
Patients with LLA events, N (%)	51 (1.1)	36 (0.7)
Incidence rate[1] (95% CI)	0.65 (0.49, 0.84)	0.46 (0.32, 0.62)
HR (95% CI); p value[2]	0.70 (0.46, 1.08); 0.1050	
Nervous system disorders		
Patients with LLA events, N (%)	66 (1.4)	72 (1.5)
Incidence rate[1] (95% CI)	0.85 (0.66, 1.07)	0.92 (0.72, 1.14)
HR (95% CI); p value[2]	1.09 (0.78, 1.52); 0.6274	
Volume depletion		
Patients with LLA events, N (%)	74 (1.5)	91 (1.9)
Incidence rate[1] (95% CI)	0.95 (0.75, 1.18)	1.16 (0.94, 1.41)
HR (95% CI); p value[2]	1.22 (0.90, 1.66); 0.1978	

1 Patients with events per 100 PY

2 Based on a Cox regression model with terms for trial, baseline diabetes status, and treatment.

Data source: PASS 1245-0171 [c32096554-01], Section 1, Table 3

Conclusions of PASS 1245-0171

In this evaluation of LLAs and AEs related to amputation in patients treated with empagliflozin compared with placebo in a pooled population of 3 long-term, randomised, clinical trials including patients with T2DM and HFpEF or HFrEF, the frequencies of LLAs were low and comparable in patients treated with empagliflozin and placebo. There was also no increased risk of AEs potentially related to LLAs. Based on the results of this meta-analysis, there is no change in the benefit-risk profile for empagliflozin.

SVII.2.1.2 PASS 1245-0137 [c37800399-01] and post-hoc meta-analysis [c40545348, c40545350]

In EMPA-KIDNEY [c37800399-01], the incidence of LLA was higher in patients treated with empagliflozin than in placebo group, but the difference did not reach statistical significance: on treatment (HR=1.80; 95% CI 0.94, 3.45), ITT (HR=1.43; 95% CI 0.80, 2.57). During treatment, more minor LLA and major LLA occurred in patients treated with empagliflozin than in the placebo group. In the ITT analysis, there were more minor LLA in patients treated with empagliflozin, and similar numbers of major LLA. More patients treated with empagliflozin had >1 episode of LLA, although the numbers were small. No particular subgroup was seen at higher risk of LLA when treated with empagliflozin compared to placebo. The results of the AEs potentially related to LLA were inconsistent with the previous studies: lower incidence of vascular AEs in patients treated with empagliflozin compared to placebo (no difference in SAF-M1) and higher incidence of AEs related to diabetic foot, infections and wound/infection (no difference in SAF-M1).

To further investigate the potential impact of treatment with empagliflozin on LLA, a post-hoc meta-analysis using patient-level data was done. The pool SAF-M3 included the 4 large, randomised, double-blind, placebo-controlled clinical trials (EMPA-REG OUTCOME 1245-0025, EMPEROR-Preserved 1245-0110, EMPEROR-Reduced 1245-0121, and EMPA-KIDNEY 1245-0137).

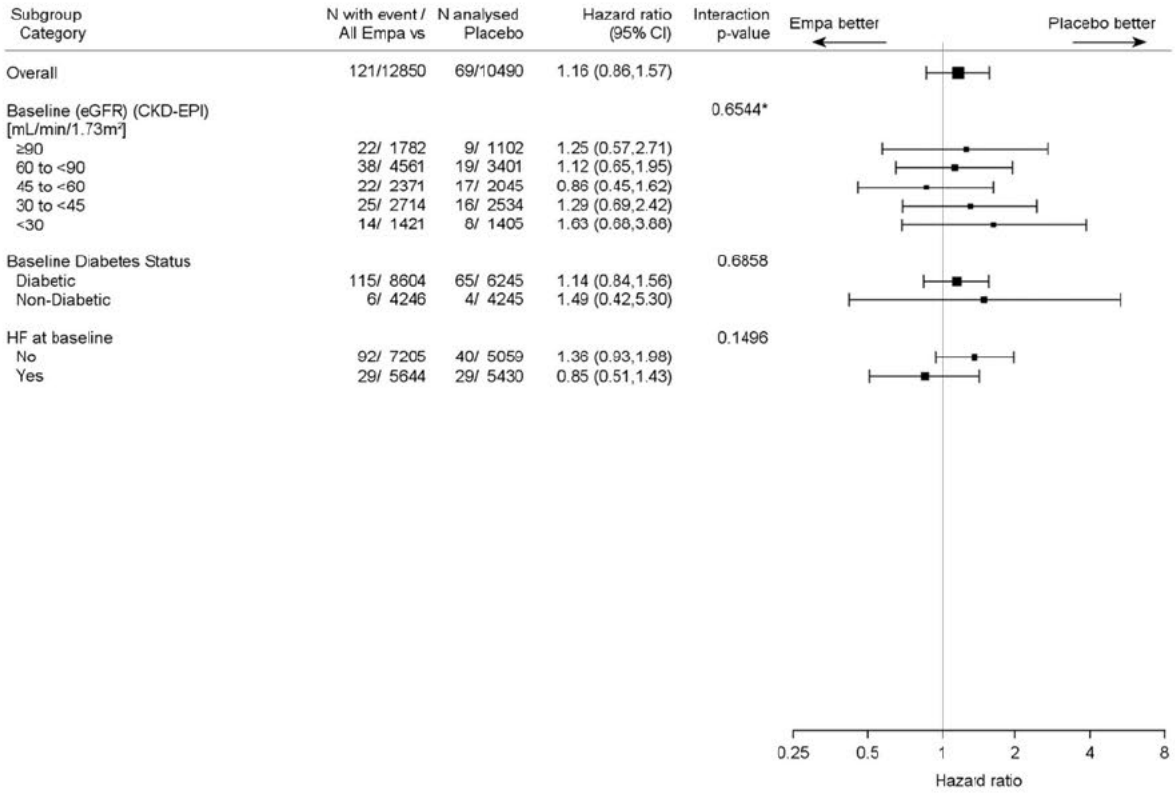
The pool SAF-M3 included a total of 23 340 randomised and treated patients. The median duration of exposure to trial drug was 1.93 years overall, 20.2 years in the all empagliflozin group, and 1.82 years in the placebo group. The total exposure was 25 823.7 PY in the all empagliflozin group and 19 526.3 PY in the placebo group (the difference in exposure was due to the additional 25 mg empagliflozin treatment group in trial 1245-0025) (SCS EMPA-KIDNEY [c40554976-01], Section 2.1.3.3)].

During treatment, no increased risk of LLA in patients treated with empagliflozin compared to placebo was seen: HR=1.16 (95% CI 0.86, 1.57). There was no statistically significant difference between the trials included in the meta-analysis: interaction p-value=0.34. The results were similar in the analysis of death as a competing risk: HR=1.17 (95% CI 0.86, 1.58) (SCS EMPA-KIDNEY [c40554976-01], Section 2.1.3.3).

In the ITT analysis, considering all the cases of LLA until the last follow-up, the HR was 1.05 (95% CI 0.81, 1.36), interaction p-value=0.38. A similar result was seen considering death as a competing risk: HR=1.06 (95% CI 0.81, 1.37) (SCS EMPA-KIDNEY [c40554976-01], Section 2.1.3.3).

The 4 trials in the post-hoc meta-analysis investigated participants with different conditions: T2DM, HF, and CKD. Each of these trials included participants with the comorbidities studied in the other trials. Subgroup comparisons of all empagliflozin vs. placebo in time to first LLA by baseline eGFR, diabetes status, and HF status are summarised in SVII.Figure 1 (on treatment) and SVII.Figure 2 (up to last follow-up).

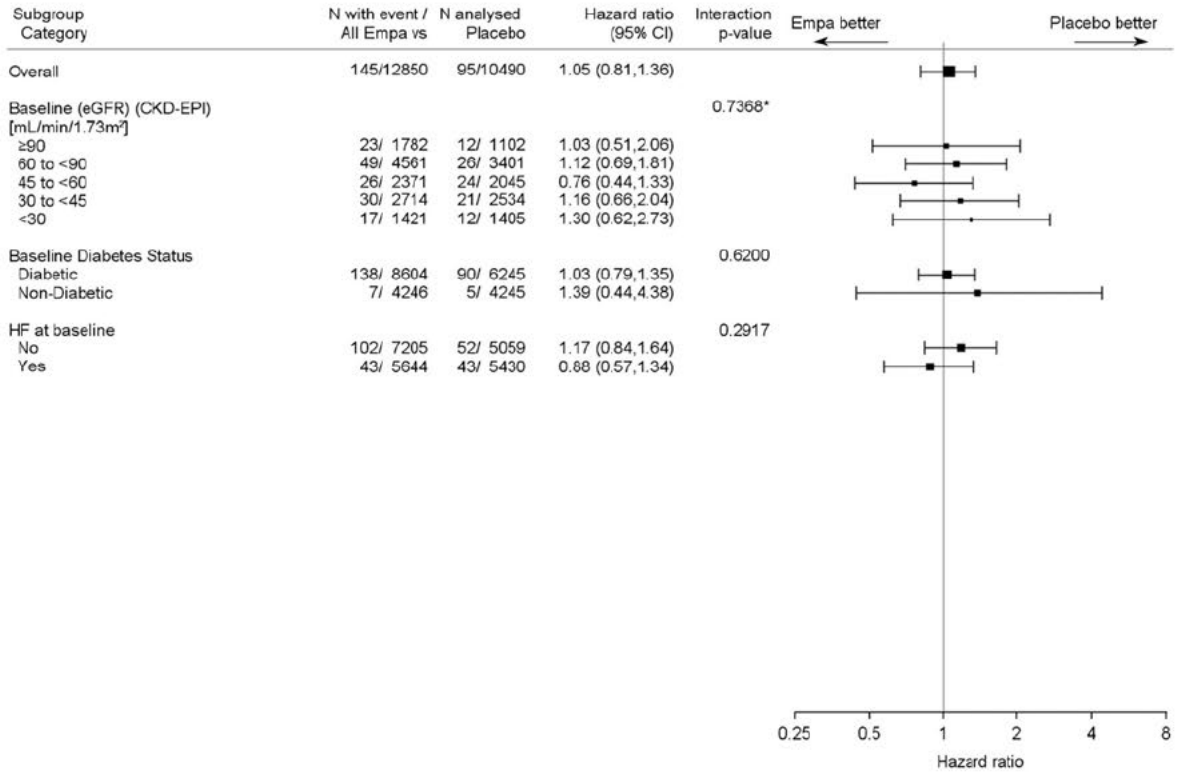
SVII.Figure 1 Forest plot of subgroup analyses of time to first LLA on treatment – TS, SAF-M3



*=Trend test

Data source: SCS EMPA-KIDNEY [c40554976-01], Figure 4

SVII.Figure 2 Forest plot of subgroup analyses of time first LLA up to last follow-up[1] – TS, SAF-M3



[1] Last follow-up refers to final follow-up visit in trial 1245-0137.

*=Trend test

Data source: SCS EMPA-KIDNEY [c40554976-01], Figure 5

AEs potentially related to amputation, including cases not leading to amputation, were identified based on the list of PTs established by the EMA as an outcome of the Article 20 referral on LLA. There was no consistent trend of increase frequency of these event categories among the 4 analysed trials (see SVII.Table 5 to SVII.Table 9).

SVII.Table 5 Participants with vascular AEs - TS

Vascular AEs	Placebo		Empagliflozin	
	n/N (%)	Rate (100/PY)	N (%)	Rate (100/PY)
1245-0025	99/2333 (4.2)	1.77	211/4687 (4.5)	1.81
1245-0110	67/2989 (2.2)	1.21	65/2996 (2.2)	1.17
1245-0121	32/1863 (1.7)	1.44	30/1863 (1.6)	1.33
1245-0137	48/3305 (1.5)	0.80	29/3304 (0.9)	0.48

Events up to first LLA included for 1245-0025, 1245-0110, and 1245-0121. All on-treatment events included for 1245-0137.

Data source: SCS EMPA-KIDNEY [c40554976-01], Table 14

SVII.Table 6 Participants with diabetic foot related AEs - TS

Diabetic foot	Placebo		Empagliflozin	
	n/N (%)	Rate (100/PY)	N (%)	Rate (100/PY)
1245-0025	43/2333 (1.8)	0.75	91/4687 (1.9)	0.76
1245-0110	21/2989 (0.7)	0.38	17/2996 (0.6)	0.30
1245-0121	4/1863 (0.2)	0.18	19/1863(1.0)	0.84
1245-0137	34/3305 (1.0)	0.57	50/3304 (1.5)	0.83

Events up to first LLA included for 1245-0025, 1245-0110, and 1245-0121. All on-treatment events included for 1245-0137.

Data source: SCS EMPA-KIDNEY [c40554976-01], Table 15

SVII.Table 7 Participants with infections - TS

Infections	Placebo		Empagliflozin	
	n/N (%)	Rate (100/PY)	N (%)	Rate (100/PY)
1245-0025	147/2333 (6.5)	2.64	257/4687 (5.5)	2.22
1245-0110	108/2989 (3.6)	1.97	97/2996 (3.2)	1.75
1245-0121	35/1863 (1.9)	1.57	42/1863 (2.3)	1.88
1245-0137	40/3305 (1.2)	0.67	51/3304 (1.5)	0.85

Events up to first LLA included for 1245-0025, 1245-0110, and 1245-0121. All on-treatment events included for 1245-0137.

Data source: SCS EMPA-KIDNEY [c40554976-01], Table 16

SVII.Table 8 Participants with wound/infections - TS

Wound/infections	Placebo		Empagliflozin	
	n/N (%)	Rate (100/PY)	N (%)	Rate (100/PY)
1245-0025	46/2333 (2.7)	1.14	132/4687 (2.8)	1.12
1245-0110	34/2989 (1.1)	0.61	27/2996 (0.9)	0.48
1245-0121	17/1863 (0.9)	0.76	9/1863 (0.5)	0.40
1245-0137	28/3305 (0.8)	0.47	39/3304 (1.2)	0.68

Events up to first LLA included for 1245-0025, 1245-0110, and 1245-0121. All on-treatment events included for 1245-0137.

Data source: SCS EMPA-KIDNEY [c40554976-01], Table 17

SVII.Table 9 Participants with nervous system disorders - TS

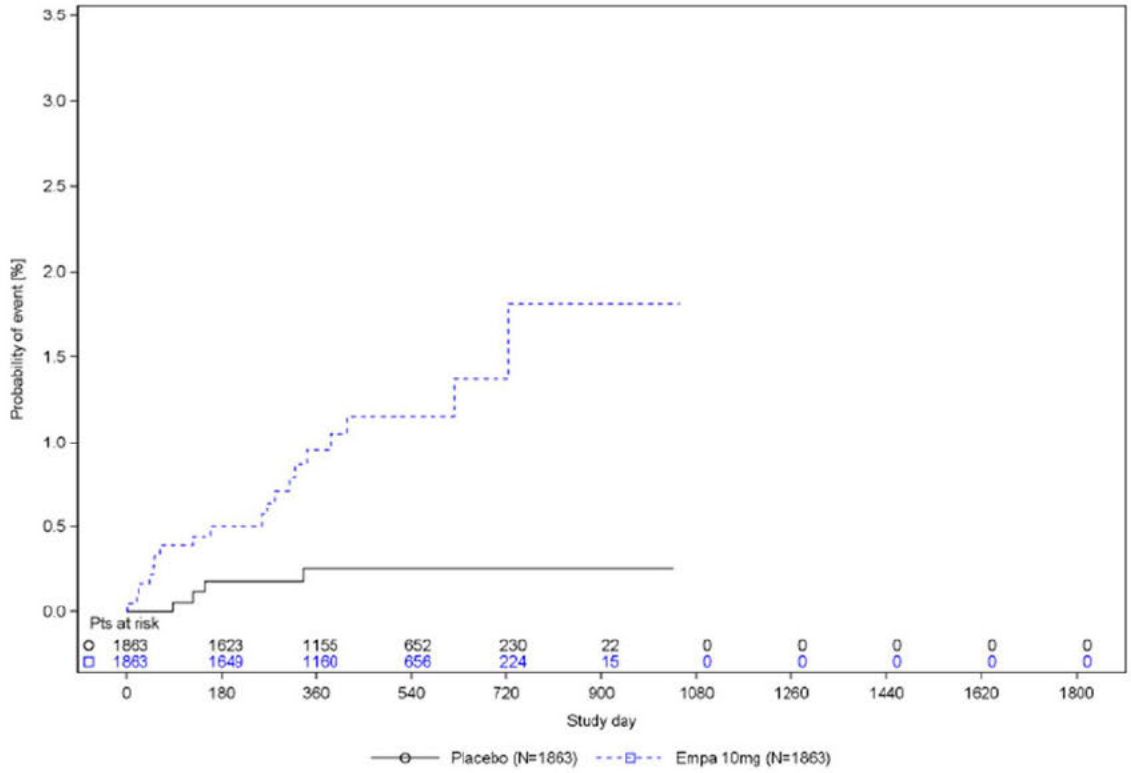
Neuropathy	Placebo		Empagliflozin	
	n/N (%)	Rate (100/PY)	N (%)	Rate (100/PY)
1245-0025	139/2333 (6.0)	2.53	277/4687 (5.9)	2.41
1245-0110	51/2989 (1.7)	0.92	55/2996 (1.8)	0.99
1245-0121	15/1863 (0.8)	0.67	17/1863 (0.9)	0.75
1245-0137	121/3305 (3.7)	2.06	119/3304 (3.6)	2.01

Events up to first LLA included for 1245-0025, 1245-0110, and 1245-0121. All on-treatment events included for 1245-0137.

Data source: SCS EMPA-KIDNEY [c40554976-01], Table 18

In trial 1245-0121, AEs related to diabetic foot were more frequently reported in the empagliflozin group. This is most probably a chance finding based on the very low frequency in the placebo group and the observation that, based on the Kaplan-Meier analysis (SVII.Figure 3), no further event occurred on placebo after 1 year of treatment, which has no plausible medical explanation. Further, there is no plausible medical explanation why empagliflozin would increase the risk of diabetic foot related AEs only in patients with HFrEF.

SVII.Figure 3 Kaplan-Meier estimate of time to first diabetic foot related AE, on treatment, trial 1245-0121 - TS



Note: Only AEs occurring before the first LLA are included. Patients with LLA are censored at time of LLA.

Data source: SCS EMPA-KIDNEY [c40554976-01], Figure 6

In all 4 trials, patients treated with empagliflozin reported slightly more frequently AEs of dehydration, which is an identified side effect of empagliflozin (SVII.Table 10).

SVII.Table 10 Participants with AEs of volume depletion[1] - TS

Volume depletion	Placebo		Empagliflozin	
	n/N (%)	Rate (100/PY)	N (%)	Rate (100/PY)
1245-0025	16/2333 (0.7)	0.28	38/4687 (0.8)	0.32
1245-0110	50/2989 (1.7)	0.90	65/2996 (2.2)	1.16
1245-0121	24/1863 (1.3)	1.08	26/1863 (1.4)	1.16
1245-0137[2]	70/3305 (2.1)	1.18	80/3304 (2.4)	1.35

[1] Volume depletion includes the PTs 'Dehydration' and 'Hypovolaemia', applicable to trials 1245-0025, 1245-0110, and 1245-0121.

[2] Symptomatic dehydration, applicable to trial 1245-0137.

Events up to first LLA included for 1245-0025, 1245-0110, and 1245-0121. All on-treatment events included for 1245-0137.

Data source: SCS EMPA-KIDNEY [c40554976-01], Table 19

There are no data suggesting an association between dehydration and occurrence of LLA. No AE of dehydration was reported before an LLA in trials 1245-0025, 1245-0110 and 1245-0121. In trial 1245-0137, an event of dehydration was reported before LLA for 2 participants: in 1 participant, dehydration occurred approximately 3 months before the LLA due to osteomyelitis; and in 1 participant, dehydration occurred >1 year before the LLA due to traumatic fracture (SCS EMPA-KIDNEY [c40554976-01], Section 2.1.3.3).

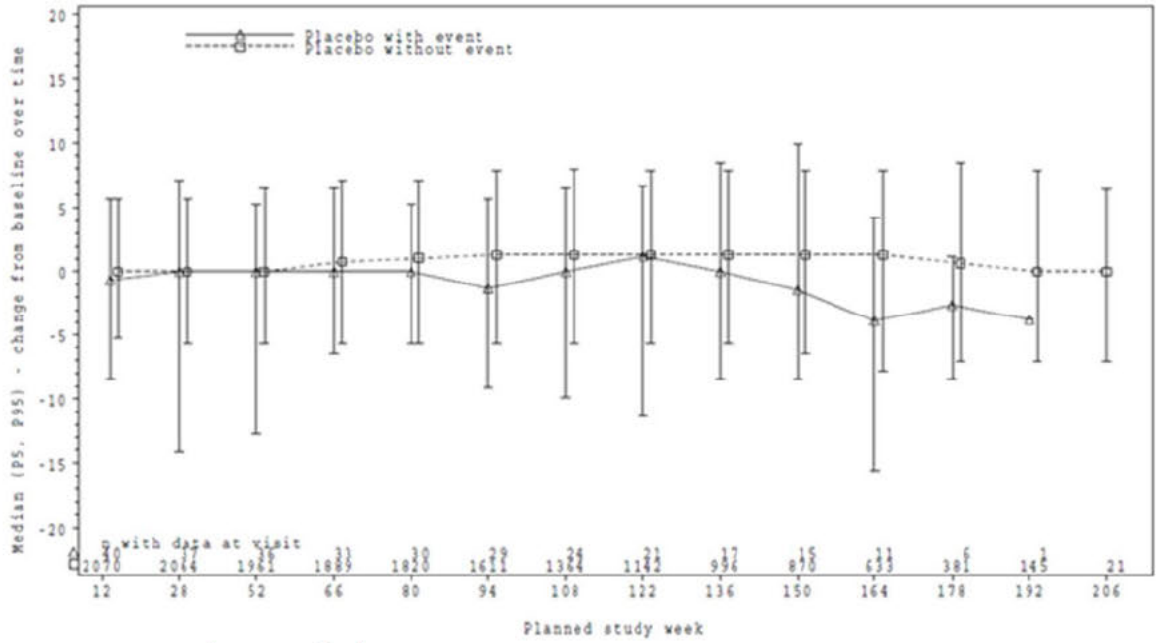
An analysis of the change from baseline of haematocrit as a surrogate marker for volume depletion was performed in patients with LLA compared to patients without LLA in trial 1245-0025 and did not indicate a correlation between haematocrit and risk of LLA (SVII.Table 11). The time course curves of the median values also did not show difference between the patients with and without lower limb amputations in any treatment arm (SVII.Figure 4 to SVII.Figure 6).

SVII.Table 11 Haematocrit values over time in patients with and without LLA, trial 1245-0025

	Placebo	Empa 10	Empa 25	All Empa
Maximal value on treatment, mean (SD), median				
Patients without LLA	42.0 (5.7), 45.2	48.9 (5.9), 49.1	49.4 (5.9), 49.1	49.1 (5.9), 49.1
Patients with LLA	43.3 (6.8), 43.5	47.8 (7.1), 49.1	46.7 (6.4), 46.5	47.2 (8.3), 42.5
Last value on treatment, mean (SD), median				
Patients without LLA	41.8 (6.0), 41.7	45.8 (6.2), 45.9	46.2 (6.2), 46.5	46.0 (6.2), 46.5
Patients with LLA	38.1 (7.0), 39.9	43.0 (7.8), 42.5	42.3 (8.8), 42.8	42.7 (8.3), 42.5

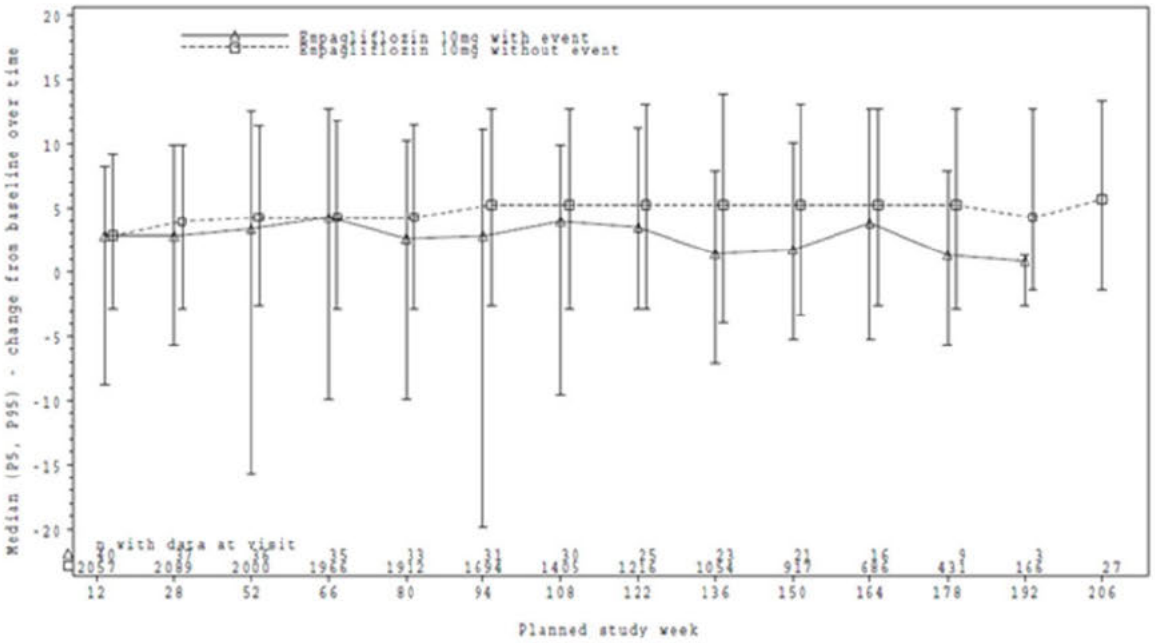
Data source: RU1043 [c40545348], Table 30.1.2.2

SVII.Figure 4 Change-from-baseline of haematocrit in patients with and without LLA, trial 1245-0025, treatment placebo, TS



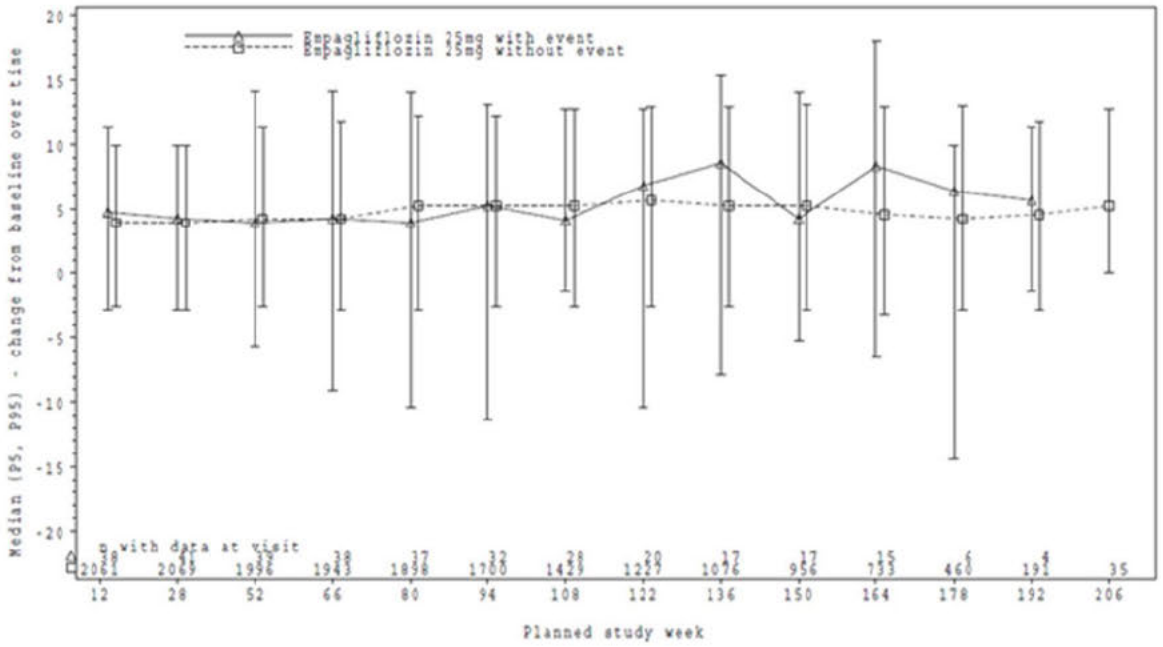
Data source: RU1062 [s00080795], Figure 48.3.1

SVII.Figure 5 Change-from-baseline of haematocrit in patients with and without LLA, trial 1245-0025, treatment empagliflozin 10 mg, TS



Data source: RU1062 [s00080795], Figure 48.3.1

SVII.Figure 6 Change-from-baseline of haematocrit in patients with and without LLA, trial 1245-0025, treatment empagliflozin 25 mg, TS



Data source: RU1062 [s00080795], Figure 48.3.1

Baseline use of diuretics, meta-analysis 1245-0171

There was no increased risk of LLA in the subgroup of patients with a baseline use of diuretics, including loop and high-ceiling diuretics, in the meta-analysis 1245-0171, in both SAF-M1 and SAF-M2 (SVII.Table 12).

SVII.Table 12 LLA according to the use of diuretics at baseline, 1245-0171

	N with events/N analysed		Hazard ratio (95% CI)	Interaction p-value
	All Empagliflozin	Placebo		
SAF-M1, on treatment				
Baseline use of diuretics				
No	37/3106	22/1773	0.85 (0.50, 1.45)	0.4153
Yes	58/6440	33/5412	1.13 (0.73, 1.75)	
Baseline use of loop or high-ceiling diuretics				
No	60/5227	33/3211	0.92 (0.60, 1.14)	0.4689
Yes	35/4319	22/3974	1.19 (0.69, 2.03)	
SAF-M2, on treatment				
Baseline use of diuretics				
No	0/542	3/468	NC	NC
Yes	18/4317	18/4384	NC	
Baseline use of loop or high-ceiling diuretics				
No	1/268	6/1244	NC	NC
Yes	17/3591	15/3608	NC	

Data source: PASS 1245-0171 [c32096554-01], Figures 15.2.2.1.1: 1 and 15.2.2.1.1: 3

Conclusion of PASS 1245-0137 and post-hoc meta-analysis

A small numerical increase in the percentage of patients with LLA was observed in the EMPA-KIDNEY trial. A post-hoc meta-analysis conducted in patients treated with empagliflozin compared with placebo in a pooled population of 4 large, randomised, clinical trials, no increased risk of LLA in patients treated with empagliflozin compared to placebo was seen. There was also no increased risk of AEs potentially related to LLAs. Based on these results, there is no change in the benefit-risk profile for empagliflozin.

SVII.2.1.3 Epidemiological and other data

In the outcome studies of other SGLT-2 inhibitors, only in the CANVAS studies of canagliflozin the risk of LLA was increased: HR=1.97; 95% CI 1.41, 2. 75 [R17-3389]. There was no increased risk in the CVOTs of dapagliflozin, ertugliflozin or sotagliflozin, and not in the renal outcome trials with canagliflozin (CREDENCE) and dapagliflozin (DAPA-CKD). A meta-analysis of all SGLT-2 inhibitor trials [P22-08594], including CANVAS, showed a statistically significant risk with HR=1.15 (95% CI 1.02, 1.30). However, the CANVAS HR of 1.97 (95% CI 1.41, 2.75) indicates a statistically significant different treatment effect (heterogeneity p for CANVAS vs. other 12 trials <0.001). When CANVAS is excluded from the meta-analysis, no statistically significant increased risk of LLA is seen: HR=1.06 (95% CI 0.93, 1.21). These results do not support the hypothesis that a common class-effect of the SGLT-2 inhibitors may be the reason of the increased risk in the CANVAS programme. The analyses to investigate the potential association between the volume

depletion and LLA in EMPA-REG OUTCOME trial (haematocrit as surrogate marker as volume depletion or AEs of volume depletion preceding the LLA) did not find supportive evidences. A non-BI sponsored NIS [R19-0843] indicated an increased risk of LLA in patients using diuretics; however, this study has severe methodological limitations to be considered as an evidence for a risk. No increased risk of LLA was found in the subgroups of patients treated with diuretics at baseline in the meta-analysis 1245-0171. Pre-clinical data rather suggest that the effect of canagliflozin may be different from empagliflozin and dapagliflozin. Canagliflozin has a higher distribution in the skin [P17-10407]. It inhibits in clinically relevant doses the cellular respiration [R13-3148, P16-11224]. This inhibition may have negative effect on the diabetic foot during tissue hypoxia.

The NIS of SGLT-2 inhibitors do not show a consistent increased risk of LLA of SGLT-2 inhibitors (except canagliflozin) compared to other antidiabetic medications. The BI-sponsored EMPRISE studies [P22-04461], including over 150 000 empagliflozin initiators did not show an increased risk of LLA of empagliflozin compared to DPP-4 inhibitors: HR=1.07; 95% CI 0.89, 1.28 in EMPRISE US [P22-04461], and HR=0.78; 95% CI 0.52, 1.17 in EMPRISE Europe and Asia [c38709052-02]. In a non-BI-sponsored study by Ueda et al [P18-10986], the risk of LLA in the combined cohort of dapagliflozin (61%) and empagliflozin (38%) was increased compared to GLP-1 agonists: HR=2.32; 95% CI 1.37, 3.91. However, a lower number of cases were included compared to CVOTs of empagliflozin: 240 in the CVOTs, 62 in the NIS. In addition, the effect of GLP-1 agonist on LLA may not be neutral, but beneficial, and therefore no conclusion can be made for the effect of SGLT-2 inhibitors from this study. The results of this observational study should be seen in relation to the data from the large, randomised, placebo-controlled CVOT of empagliflozin, which are considered as gold standard for assessing the causality for events with multiple risk factors, such as LLA.

SVII.2.1.4 Overall conclusion

No increased risk of LLA was seen in patients treated with empagliflozin. The data do not support that a common class-effect (e.g. dehydration) could explain the increased risk of LLA seen in the CANVAS studies with canagliflozin. No additional pharmacovigilance activities or additional risk minimisation measures are planned. In line with GVP Module V Rev 2, it is proposed:

- To demote this safety concern from the EU-RMP
- To further monitor this topic in the PBRER
- To no longer collect additional information about cases of LLA outside clinical trials with a dedicated questionnaire
- To consider LLA no longer as AESI in new studies, with the need to collect additional information about these events

SVII.2.2 Changes in the safety concerns from v20.0

Based on the results of PASS 1245-0096, BI proposes to remove 'Complicated UTI', 'Genital infection', and 'DKA with atypical presentation' as important identified risks and 'Liver injury' as important potential risk from the RMP.

SVII.2.2.1 Removal of the important identified risk 'Complicated urinary tract infection'

BI proposes to remove the important identified risk 'Complicated UTI' from the list of safety concerns, based on the following rationale:

- No studies are ongoing to further characterise safety information on this topic.
- The clinical trial data in T2DM did not show an increased incidence of complicated UTI, namely serious events and events within the scope of pyelonephritis, except of a numerical imbalance for urosepsis. Thus, a limited number of patients experienced urosepsis in clinical trials. Cases of pyelonephritis and urosepsis were reported; in some of them, no predisposing condition was reported. The frequency of patients with complicated UTI was higher in all treatment groups in female patients, in patients with renal impairment, in patients aged >75 years, and in patients with a history of UTI.
- In clinical trials with empagliflozin in the HF clinical programme, the frequency of patients with complicated UTI was similar between both treatment groups; results of subgroup analyses were in general similar to the main analysis.
- The clinical trial data of empagliflozin are in agreement with the known risk factors for UTI:
    - Female gender
    - Sexually active females tend to have more UTIs than women who are not sexually active
    - Females who use diaphragms for birth control may be at higher risk, as may women who use spermicidal agents
    - After menopause, UTIs may become more common because the lack of oestrogen causes changes in the urinary tract that make it more vulnerable to infection
    - Kidney stones may be associated with an increased risk of complicated UTIs
    - Prostatic enlargement may be associated with urinary retention in the bladder may increase the risk of UTI in males
    - Diabetes and other diseases that impair the immune system may increase the risk of UTIs
    - Instrumentation with a catheter to urinate may increase the risk of UTIs
    - Asymptomatic bacteriuria

- In PASS 1245-0096 (Post-authorisation safety study in patients with type 2 diabetes mellitus to assess the risk of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infection, genital infections, and diabetic ketoacidosis among patients treated with empagliflozin compared with patients treated with DPP-4 inhibitors), data demonstrated that the IR of severe complications of UTI per 1000 PY among initiators of empagliflozin was about half the IR among initiators of DPP-4 inhibitors. Similarly, the crude and adjusted IRRs of severe complications of UTI showed 50% less risk among initiators of empagliflozin than among initiators of DPP-4 inhibitors [c40420600-01]. Severe complications of UTI included pyelonephritis and urosepsis. These were uncommon events (≥1 per 1000 to <1 per 100) but less frequent among initiators of empagliflozin who had a 49% decreased risk compared with initiators of DPP-4 inhibitors. Although SGLT-2 inhibitors have been hypothesised to potentially increase the risk of UTIs due to mechanisms including glucosuria, others have hypothesised that SGLT-2 inhibitor-induced diuresis and polyuria may counteract any expected bacterial growth due to glucosuria [R22-3252]. The present study may have some degree of unmeasured confounding that may explain the observed decreased risk of severe complications of UTI. The quantitative bias analysis for severe complications of UTI was conducted considering "instructions of physicians to increase hydration among patients using SGLT2 inhibitors" as a potential unmeasured confounder. An extreme confounding scenario could bring the measured IRR close to the null. The decreased risk of severe complications of UTI, may be explained by SGLT-2 inhibitor-induced diuresis and polyuria, which counteract the expected increased bacterial growth due to glucosuria, thereby reducing bacterial load in urine and/or preventing ascension of bacteria through the urinary tract. This increased urinary flow attenuates over time (days to 12 weeks) and may explain the higher risk observed in trial with longer duration of follow-up [R22-2428], although no differences by duration of use (more or less than 6 months) were observed in this study.
- Summary of post-marketing data

  In the cumulative post-marketing data (DLP 17 Apr 2022) presented in the latest combined Jardiance/Synjardy PBRER [s00106777-01], 753 cases reporting 818 events pertaining to complicated UTIs were identified. There were 11 cases reported in which complicated UTI was reported as fatal event.

  In approximately 29% of the cases, known risk factors for complicated UTI (e.g. obesity, alcohol use, smoking, poor hygiene, etc.) and history of recurrent genital infections and UTI were reported. In the remaining cases, limited information regarding concomitant diseases precluded an adequate medical assessment. It should be considered that T2DM itself is a risk factor for UTIs.

  UTIs are a common comorbidity in patients with diabetes. Observational studies in patients with diabetes and infection suggest that they seem to be more likely to progress to bloodstream infections and sepsis than in patients with infection but no diabetes [R10-6634, R12-5224]. The IR of various UTIs in T2DM patients in Europe and North America between 1990 and 2011 were between 46.9 and 101 per 1000 PY [R14-0268, R12-5226, R12-1105]. The IR of pyelonephritis in T2DM was between 3 and 4.9 per 1000 PY [R12-1105, R10-6632].

Complicated UTI often leads to hospitalisation. The IR of serious UTI and pyelonephritis were similar in patients treated with empagliflozin and placebo; therefore, no public health impact is expected. The IR of urosepsis was higher in patients treated with empagliflozin; however, the number of cases was limited to allow public health impact assessment. Evidence from observational studies suggests that there is no public health impact of complicated UTI in patients treated with empagliflozin compared to patients treated with DPP-4 inhibitor or GLP-1 receptor agonist [P19-07703].

Conclusion

Complicated UTIs including pyelonephritis and urosepsis are a class risk of SGLT-2 inhibitors and are included as side effects in the EU PI for empagliflozin-containing products. In addition, the EU PI includes in the section 'Special warnings and precautions' a recommendation to consider a temporary interruption of treatment with empagliflozin in case of occurrence of a complicated UTI.

In line with the GVP Module V recommendations, there is no reasonable expectation that existing or future feasible pharmacovigilance activities could further characterise the safety profile of empagliflozin with respect to complicated UTI. BI therefore proposes the removal of 'Complicated UTI' as an important identified risk from the RMP.

SVII.2.2.2 Removal of the important identified risk 'Genital infection'

BI proposes to remove the important identified risk 'Genital infection' from the list of safety concerns based, on the following rationale:

- No studies are ongoing to further characterise safety information on this topic.
- Clinical trial data in the T2DM population demonstrated that the percentage of patients with genital infection was higher in the empagliflozin 10/25 mg than in the placebo group: 5.6% vs. 1.5%, respectively. The incidence rate ratio and risk ratio for empagliflozin 10/25 mg vs. placebo favoured placebo. The percentage of patients with serious genital infection was low and comparable between treatment groups (both 0.1%), all but 1 (immediately life-threatening event) requiring or prolonging hospitalisation. There were no fatal events. The percentage of patients with genital infection leading to treatment discontinuation was low, but higher in the empagliflozin 10/25 mg group (0.5%) than in the placebo group (<0.1%). The reported genital infections were mainly of mild to moderate severity; few patients had severe events. The majority of patients with genital infection recovered.
- HFpEF clinical trial data demonstrated that the percentage of patients with genital infection was higher in the empagliflozin 10 mg group than in the placebo group: 2.2% vs. 0.7%, respectively. The incidence rate ratio and risk ratio favoured placebo (incidence rate for empagliflozin 10 mg: 1.23/100 PY vs. placebo: 0.39/100 PY). Only few events in both groups were serious, mostly required prolonged hospitalisation. Most events in the placebo group were of mild intensity, in the empagliflozin 10 mg group of mild or moderate intensity. Most patients had recovered from the event at the time of database lock. There were no fatal events.

- HFrEF clinical trial data showed that the percentage of patients with genital infection was higher in the empagliflozin 10 mg group than in the placebo group: 1.6% vs. 0.6%, respectively. The incidence rate ratio and risk ratio favoured placebo (incidence rate for empagliflozin 10 mg: 1.40/100 PY vs. placebo: 0.57/100 PY). All but 1 event in the placebo group required/prolonged hospitalisation. The events were of mild or moderate intensity with similar proportions in either treatment group or most patients had recovered from the event. There were no fatal events.
- The clinical trial data of empagliflozin are in agreement with the known risk factors for genital infection:
    - Female gender
    - Sexually active females tend to have more genital infections than women who are not sexually active
    - Females who use diaphragms for birth control may be at higher risk, as may women who use spermicidal agents
    - After menopause, genital infections may become more common because the lack of oestrogen causes changes in the genital that make it more vulnerable to infection
    - Diabetes and other diseases that impair the immune system may increase the risk of genital infection

- In PASS 1245-0096 (Post-authorisation safety study in patients with type 2 diabetes mellitus to assess the risk of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infection, genital infections, and diabetic ketoacidosis among patients treated with empagliflozin compared with patients treated with DPP-4 inhibitors), data demonstrated that the IR of genital infection per 1000 PY among initiators of empagliflozin was more than 4-times higher than the IR among initiators of DPP-4 inhibitors in both males and females. Similarly, the crude and adjusted IRRs for genital infection among males showed a 4-fold increased risk among initiators of empagliflozin compared with initiators of DPP-4 inhibitors. Female initiators of empagliflozin had a 3-fold increase in the risk of genital infection compared with initiators of DPP-4 inhibitors. It is important to note that severe genital infections in this study are defined as hospitalisation for genital infection or systemic treatment with antifungals or antibiotics (as opposed to topical or vaginal treatment). The majority of cases categorised in the severe genital infection category are those with systemic treatment for antibacterial or antifungals which were the majority since guidelines recommend that genital infection in patients with T2DM be treated with systemic medications [c40420600-01].
- Summary of post-marketing data

  In the cumulative post-marketing data (DLP 17 Apr 2022) presented in the latest combined Jardiance/Synjardy PBRER [s00106777-01], 4070 cases reporting 4273 events pertaining to genital infection were identified for all indications. The majority of cases were from spontaneous reporting. There were no fatal genital

infections. More than half of the cases (55.3%) had no reported outcome. In the remaining cases, most of them recovered (29.4%). In the recovered events with treatment status reported, genital infection treatment was administered to 585 events, not administered to 43 events, and unknown for 636 events.

Considering the 4070 cases, 8.3% of these cases had known risk factors for genital infection (e.g. obesity, alcohol use, smoking, poor hygiene, etc.) and/or history of recurrent genital infections reported. Most of the cases had missing information regarding co-morbidity (74%) or limited information provided concerning risk factors for genital infections (17.7%). Nevertheless, it should be considered that T2DM itself is a risk factor for genital infection and only 17 patients out of 4070 (0.5%) had HF as the exclusive indication for Jardiance.

Information on incidence estimates for genital infections in patients with T2DM is very limited and is not available for most countries other than the UK and US, although they seem to be rather common. Available data in T2DM suggests the incidence of male genital infections is between 8 and 13 per 1000 PY, and female genital infections between 2 and 21 per 1000 PY, with reasons for this discrepancy yet to be clarified [R13-3872, R10-6632].

Overall, the cumulative data do not point to an increased severity or higher specificity of the important identified risk of genital infection in patients with T2DM as well as in non-diabetic patients who were receiving empagliflozin for a HF indication.

Conclusion

Patients with genital infection generally recover after ambulatory treatment without permanent consequences, not requiring further health care system resource utilisation. Genital infection is considered a class-effect for all SGLT-2 inhibitors. The EU PI for empagliflozin-containing products correctly reflect the current knowledge regarding the risk of genital infection and no amendments are currently warranted. In line with the GVP Module V recommendations, there is no reasonable expectation that existing or future feasible pharmacovigilance activities could further characterise the safety profile of Jardiance with respect to genital infection. BI therefore proposes the removal of 'Genital infection' as an important identified risk from the RMP. In addition, the topic 'Complicated genital infection' will continue to be monitored in the PBRER.

SVII.2.2.3 Removal of the important identified risk 'Diabetic ketoacidosis with atypical presentation'

BI proposes to remove the important identified risk 'DKA with atypical presentation' from the list of safety concerns, based on the following rationale:

- No studies are ongoing to further characterise safety information on this topic.
- Clinical trial data of empagliflozin in the T2DM trials did not show an increased risk of DKA. In the randomised, double-blind, placebo-controlled trials (SAF-43), the percentage of patients with DKA was low and comparable across treatment groups (both 0.1%). The incidence rate ratio and risk ratio for empagliflozin 10/25 mg vs. placebo suggested no substantial differences between the treatment groups. The

percentage of patients with serious DKA events was low (≤1.0%), with most of the events requiring hospitalisation. There were no fatal events. 2 patients in the empagliflozin 10/25 mg group discontinued treatment due to DKA. No clear pattern towards intensity of the events was noted in either treatment group. All but 1 patient in the empagliflozin 10/25 mg group had recovered from the event.

- In clinical trials with empagliflozin in the HF clinical programme HFpEF, the percentage of patients with diabetic ketoacidosis was low and similar between both treatment groups: 0.2% placebo vs. 0.1% empagliflozin 10 mg. All events were serious and mostly requiring/prolonging hospitalisation. The events were equally of mild, moderate, or severe intensity and most patients had recovered from the event at the time of database lock. 1 event in the empagliflozin 10 mg was fatal; only 1 event of ketoacidosis was reported from a patient without diabetes mellitus in the placebo group. All other events were derived from patients with diabetes at baseline.
- In clinical trials with empagliflozin in the HF clinical programme HFrEF, no patients with DKA or ketoacidosis were reported.
- In PASS 1245-0096 (Post-authorisation safety study in patients with type 2 diabetes mellitus to assess the risk of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infection, genital infections, and diabetic ketoacidosis among patients treated with empagliflozin compared with patients treated with DPP-4 inhibitors), a meta-analysis demonstrated that the IRR from each data source also resulted in a 2-fold increased risk of DKA among initiators of empagliflozin compared with initiators of DPP-4 inhibitors, with an adjusted IRR of 2.19 (95% CI 1.74, 2.76) for both the random-effects and the fixed-effects models [c40420600-01]. When compared with initiators of DPP-4 inhibitors, a 70% increased risk of DKA among users of SGLT-2 inhibitors was observed in a large US observational claims study [P21-10532], which is also in line with prior observational studies showing a 2-fold increased risk [R18-1215]. Published literature suggests that DKA among users of SGLT-2 inhibitors is usually atypical DKA that debuts without hyperglycaemia [R15-3150, P15-08785] and is frequently associated with recent surgery [R22-2428]. In the current study, in HIRD, 19% of confirmed cases in the empagliflozin exposure group had recent surgery, compared with 8% in the DPP-4 inhibitors exposure group. Euglycaemic DKA and ketosis may occur as a consequence of non–insulin-dependent glucose clearance, hyperglucagonemia, and volume depletion. Increased hepatic glucose production, insulin resistance related to free fatty acids, and unchecked lipolysis may be exacerbated by use of SGLT-2 inhibitors in the setting of acute conditions such as surgery. In addition, SGLT-2 inhibitors are diuretics, and their use could worsen volume depletion and starvation ketosis [R15-3150].
- In PASS 1245-0146 (A 5-year enhanced pharmacovigilance surveillance initiative to survey and characterise spontaneous occurrence and experience of ketoacidotic events in patients treated with empagliflozin-containing products), the cumulative reporting rate of DKA events across all 4 empagliflozin-containing products included in this final report, 1.7 cases/10 000 PY, was lower than the background rate of DKA in patients with T2DM independent of SGLT-2 inhibitor therapy. The available

information on predisposing conditions and precipitating factors was consistent with the current knowledge about DKA risk, such as low carbohydrate or ketogenic diet and alcohol abuse as predisposing conditions, and acute febrile infection/illness, dehydration, recent history of gastrointestinal disease, and missed/changed insulin dose as common precipitating factors for DKA. Information on time from treatment initiation to onset of ketoacidosis and duration of the ketoacidosis event was limited for most of the cases which was expected considering the acknowledged limitations associated with spontaneous reporting. The results of the final cumulative report were line with the current knowledge on DKA in relation to SGLT-2 inhibitor use in patients with T2DM, including the results from randomised controlled clinical trials with empagliflozin [c36445482-01].

- Summary of post-marketing data

  In the cumulative post-marketing data (DLP 17 Apr 2022) presented in the latest combined Jardiance/Synjardy PBRER [s00106777-01], 4063 cases were identified reporting 4108 events (including 4024 SAEs) of DKA. The majority of cases were from spontaneous reporting, and 56 fatal cases with event attribute (56 fatal events) of DKA were reported for Jardiance. The cases were reported from various countries and regions without an identifiable pattern.

  Based on post-marketing experience, the risk of DKA with SGLT inhibitor therapy for the treatment of patients with T2DM was identified. No imbalance in DKA events was seen in clinical trials with empagliflozin in patients with T2DM, but DKA was subsequently included in SGLT-2 inhibitor labels based on post-marketing reports due to the potential to induce ketogenesis through several pathophysiological mechanisms. The information on atypical presentation of DKA under empagliflozin treatment of T2DM patients, the possibility of a fatal outcome and the predisposing factors, and potential risk factors to mitigate the risk are included in the EU PI.

  Pre-clinical and clinical data show that treatment with empagliflozin increased blood ketone levels. During post-marketing, cases of DKA were reported. Epidemiological data show that the risk of DKA is higher in patients treated with SGLT-2 inhibitors [P17-04512]. DKA with atypical presentation is a class-effect of all SGLT-2 inhibitors. In situations with predisposing factors, temporary treatment interruption of empagliflozin may be required. In these situations, monitoring of ketones should be considered, even if empagliflozin treatment has been interrupted. DKA can be severe and even fatal.

Conclusion

In line with the GVP Module V recommendations, there is no reasonable expectation that existing or future feasible pharmacovigilance activities could further characterise the safety profile of Jardiance with respect to DKA with atypical presentation. BI therefore proposes the removal of 'DKA with atypical presentation' as an important identified risk from the RMP.

SVII.2.2.4 Removal of the important potential risk 'Liver injury'

BI proposes to remove the important potential risk 'Liver injury' from the list of safety concerns, based on the following rationale:

- No studies are ongoing to further characterise safety information on this topic.
- In double-blind, placebo-controlled trials for T2DM, the percentage of patients with liver injury was comparable across treatment groups with 3.2% in the placebo and 2.4% in the empagliflozin 10/25 mg group. The incidence rate ratio and risk ratio for empagliflozin 10/25 mg vs. placebo suggested insubstantial differences between the treatment groups. The frequency of serious liver injury was low (≤0.2%) and comparable between the treatment groups. Most serious events required or prolonged hospitalisation or were serious due to 'other' reason. There were no fatal events. The percentage of patients with liver injury leading to treatment discontinuation was low (≤0.3%) and comparable across the treatment groups. The reported liver injury AEs were mainly of mild severity with no apparent differences in frequency between the treatment groups; this was also the case for the moderate and severe events. Most of the patients in each treatment group had either recovered or not yet recovered from the event.

  In clinical trials for T2DM, more patients treated with empagliflozin than with placebo were reported with ALT and/or AST elevations of >5x ULN. However, the overall occurrence of liver injuries in patients treated with empagliflozin was not increased. An overview is given in the table below.

SVII.Table 13 Frequency of patients with elevated liver enzymes (SAF-43) - TS

	Placebo	**Empagliflozin 10/25 mg**
	N (%)	**N (%)**
Number of patients	4904 (100.0)	10177 (100.0)
ALT and/or AST ≥3x ULN	65 (1.3)	99 (1.0)
ALT and/or AST ≥5x ULN	11 (0.2)	40 (0.4)
ALT and/or AST ≥10x ULN	4 (0.1)	14 (0.1)
ALT and/or AST ≥20x ULN	3 (0.1)	5 (<0.1)
ALT and/or AST ≥3x ULN with total bilirubin ≥2x ULN[1]	2 (<0.1)	10 (0.1)
ALP <2x ULN[2]	1 (<0.1)	6 (0.1)
ALP ≥2x ULN[2]	1 (<0.1)	4 (<0.1)

A patient with ALT and/or AST elevation will be counted in all applicable categories. Patients are presented regardless of baseline elevations.

[1] Patients with ALT and/or AST ≥3x ULN with concomitant or subsequent total bilirubin ≥2x ULN in a 30-day period after ALT and/or AST elevation.

[2] ALP is the maximum value in the 30-day period.

Data source: Jardiance/Synjardy PBRER (reporting interval 18 Apr 2021 to 17 Apr 2022 [s00106777-01], Table 126)

Biochemical Hy's law laboratory constellation
12 patients had laboratory values consistent with biochemical Hy's law constellation (ALT and/or AST ≥3x ULN with concomitant or subsequent total bilirubin ≥2x ULN within 30 days after ALT/AST elevation, regardless of ALP value on-treatment in the empagliflozin group). These cases did not satisfy Hy's law because alternative causalities were present. All other cases of liver enzyme elevation could also be explained by plausible alternative causalities; there was no evidence of a causal relationship between empagliflozin treatment and DILI.

- In EMPEROR-Reduced, the percentage of patients with liver injury was comparable between both treatment groups with 4.5% in the placebo and 3.9% in the empagliflozin 10 mg group. The incidence rate ratio and risk ratio suggested insubstantial differences between both treatment groups. (Incidence rate for empagliflozin 10 mg: 3.51/100 PY vs placebo: 4.04/100 PY). The frequency of serious liver injury was low (≤0.9%) and similar in both treatment groups. Most of the events required/prolonged hospitalisation or were serious due to 'other medical reasons'; there were no fatal events. The percentage of patients with liver injury leading to treatment discontinuation was low (≤0.2%) and comparable between both treatment groups. The reported liver injury AEs were mainly of mild or moderate severity with no apparent differences in frequency between both treatment groups; this was also the case for the severe events.
- The frequency of patients with liver enzyme elevations was comparable between both treatment groups.
- In EMPEROR-Preserved, the percentage of patients with liver injury was comparable between both treatment groups with 5.0% in the placebo and 3.7% in the empagliflozin 10 mg group. The incidence rate ratio and risk ratio do not suggest substantial differences between both treatment groups (incidence rate for empagliflozin 10 mg: 2.11/100 PY vs placebo: 2.87/100 PY). The frequency of serious liver injury was low (≤1.3%) and similar in both treatment groups. Most of the events required/prolonged hospitalisation or were serious due to 'other medical reasons'. The percentage of patients with liver injury leading to treatment discontinuation was low (≤0.3%) and comparable between both treatment groups. The reported liver injury AEs were mainly of mild or moderate intensity.
- The frequency of patients with liver enzyme elevations was comparable between both treatment groups.
- In PASS 1245-0096 (Post-authorisation safety study in patients with type 2 diabetes mellitus to assess the risk of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infection, genital infections, and diabetic ketoacidosis among patients treated with empagliflozin compared with patients treated with DPP-4 inhibitors), data demonstrated the number of ALI1 events was numerically lower in all data sources. In all data sources, the crude IRs of ALI1 per 1000 PY were lower among initiators of empagliflozin (ranging from 0.32 to 1.32) than among initiators of DPP-4 inhibitors (ranging from 1.10 to 1.77). Similarly, for all data sources the adjusted IR of ALI1 among empagliflozin initiators (ranging from <0.01 to 1.21) was lower than the adjusted IR of ALI1 among DPP-4 inhibitor

initiators (ranging from <0.01 to 1.41) The number of ALI2 events was also low in all data sources. In all data sources, the crude IRs per 1000 PY were lower among initiators of empagliflozin (range 1.11 to 4.24) than among initiators of DPP-4 inhibitors (range 2.01 to 5.65). Similarly, the adjusted IR of ALI2 among empagliflozin initiators (range 1.23 to 4.19) was lower than the IR of ALI2 among DPP-4 inhibitor initiators (range 1.86 to 5.47). The pooled adjusted IRR was 0.70 (95% CI 0.56, 0.88) for the random-effects model, which was similar to the pooled adjusted IRR for ALI1 which showed a decreased numerical risk but was not statistically significant. Liver events (ALI1 and ALI2) were uncommon events (≥1 per 1000 to <1 per 100) in both exposure cohorts (empagliflozin and DPP-4 inhibitors).

The observed decreased risk of ALI1 and ALI2 is in line with empagliflozin's described effect on ALT levels in people with T2DM, which is further supported by the evaluation of liver enzyme elevations irrespective of ALI diagnoses. These analyses showed that elevation of ALT was infrequent, most frequently less than 5x ULN, and more common in the DPP-4 inhibitors cohort than in the empagliflozin cohort in all data sources. Results showing that elevation of liver enzymes, irrespective of ALI diagnosis was more common among patients in the DPP-4 inhibitors cohort than among patients in the empagliflozin cohort[c40420600-01].

Summary of post-marketing data
In the cumulative post-marketing data (DLP 17 Apr 2022) presented in the latest combined Jardiance/Synjardy PBRER [s00106777-01], 440 cases of liver injury were identified reporting 526 events (including 152 SAEs). There were 34 cases containing 35 events considered to be of "potential high individual impact" based on the reported hepatic event (PTs) of DILI, hepatic failure, acute hepatic failure, hepatic coma, oesophageal varices haemorrhage, hepatotoxicity, liver injury and liver transplant. In these cases, alternative explanations for the reported hepatic disorder and/or confounding factors such as concomitant or co-suspect medicines were reported, or the case was too poorly documented for causality evaluation.
Of cases reporting the PT 'Drug-induced liver injury', there was no case reported with positive rechallenge, and cases with positive dechallenge contained confounding factors. Review of cases showed either presence of confounding factors, such as pre-existing hepatic disorders, co-medications with potential impact on liver enzymes, alternative explanations, or limited information with missing or incomplete data concerning co-medications, comorbidity, clinical circumstances, or temporal association.
No risk factors specific to patients treated with empagliflozin are known. For DILI in general, risk groups include patients on hepatotoxic drugs (such as non-steroidal anti-inflammatories, carbamazepine, isoniazid, and statins), with chronic liver disease (such as fatty liver disease and viral hepatitis infections), and with diabetes.

Conclusion
In line with the GVP Module V recommendations, there is no reasonable expectation that existing or future feasible pharmacovigilance activities could further characterise the safety profile of Jardiance with respect to liver injury. BI therefore proposes the removal of 'Liver

injury' as an important potential risk from the RMP. BI also proposes the removal of 'Liver injury' as an important potential risk from the PBRER.

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 the following table.

SVII.Table 14 Overview of safety analysis sets

SAF/trial	Description	Trials included	MedDRA version
Trial 1218-0091[1]	Randomised, placebo-controlled clinical trial in paediatric patients (DINAMO)	1218-0091	25.0
Trial 1245-0137[2]	Randomised, double-blind, placebo-controlled clinical trial in patients with chronic kidney disease (EMPA-KIDNEY)	1245-0137	25.0
SAF-HF4	Randomised, placebo-controlled clinical trials in patients with HFpEF	1245-0110, 1245-0148 (HFpEF arm), 1245-0167	23.1
SAF-HF5[3]	Randomised, placebo-controlled clinical trials in patients with HFrEF	1245-0121, 1245-0168	23.0
SAF-43[4]	Randomised, double-blind, placebo-controlled trials in patients with T2DM	1245-0004, 1245-0009, 1245-0010, 1245-0015, 1245-0019, 1245-0020, 1245-0023 (Met only and Met+SU), 1245-0025, 1245-0029, 1245-0033, 1245-0035, 1245-0036, 1245-0038, 1245-0048, 1245-0049, 1245-0107, 1275-0009, 1275-0019, 1276-0010	21.0

[1] For the analysis of medical concepts for paediatric patients in the RMP, only trial 1218-0091 is used. 1245-0087 is a single dose trial and does not provide relevant information on exposure and medical concept analyses; therefore, it is not included either in exposure or in medical concept analyses for this RMP.

[2] Safety data collection was streamlined in trial 1245-0137, therefore not all AEs were collected. SAEs and pre-specified non-serious AEs were assessed (all AEs were collected in Japanese patients). Information on severity (intensity) is not provided; no subgroup analyses were performed for the RMP.

[3] Data from trial 1245-0148 was not available at the time of database lock for the HFrEF submission; the trial is therefore not included in the pooling.

4 The data of extension trial 1245-0031 are contained in the core trials 1245-0019, 1245-0020, and 1245-0023.

Data source: Trial 1218-0091: data on file, rmp-output-paediatric, Table 15.2.1: 1; Trial 1245-0137: data on file, rmp-output-ckd, Table 15.1.1: 1; SAF-HF4: data on file, SAF-HF4 (HFpEF), Table 1.1; SAF-HF5: data on file, HFrEF(SAF-HF5), Table 1.1, and SAF-43: Jardiance/Synjardy PBRER (reporting interval 18 Apr 2018 to 17 Apr 2019) [s00077934-01], Table 78

There are no important identified risks for Jardiance.

SVII.3.1.1 Important potential risk: Urinary tract carcinogenicity

SVII.3.1.1.1 Potential mechanisms

There is no established potential mechanism regarding the use of SGLT-2 inhibitors and the occurrence of malignancies. There is no established class risk for the occurrence of malignancies with SGLT-2 inhibitor use.

Clinical data with empagliflozin has not identified or established a potential mechanism for the development of malignancies.

SVII.3.1.1.2 Evidence source and strength of evidence

The potential risk of renal cancer is based on toxicology findings and bladder cancer due to observations from other SGLT-2 inhibitors:

1. Dapagliflozin data showed an imbalance for human bladder cancer (and previously also breast cancer) as presented at the US FDA Advisory Committee and also in the EPAR on dapagliflozin (EMA homepage). However, the recently finished DECLARE-TIMI 58 trial, the largest dapagliflozin phase IIIb randomised, double-blind, placebo-controlled CVOT, including more than 17 000 patients showed no imbalance with dapagliflozin vs. placebo in bladder cancer (0.3% vs. 0.5%).
2. Carcinogenicity studies with empagliflozin showed occurrence of renal malignancy in male CD-1 mice, not in female mice. The CD-1 mouse strain is characterised by increased background of renal malignancy. The empagliflozin-related renal tumours occurred only in male mice given 1000 mg/kg/day, which resulted in systemic exposure approximately 30-fold higher than exposure associated with the 25 mg/day dose in humans. Carcinogenicity studies in the rat did not reveal renal malignancy. Empagliflozin is not genotoxic. Research into the mode of action for the male mouse renal tumours revealed them to be secondary to several sources of chronic and persistent tubular degeneration [U13-3693-02]. These sources include a natural predisposition of the aged male mouse to renal pathology, exacerbation of background renal tubular dilatation and cystic hyperplasia induced by chronic osmotic diuresis, metabolic stress due to a predominantly oxidative metabolism, production of a cytotoxic metabolite predominant in the male mouse, and consequent exhaustion of tubular epithelial oxidative detoxication. Reparative tubular epithelial cell proliferation is observed in male mice but not female mice, indicating the specificity of the sequence of events for the male CD-1 mouse. Ultimately over the course of 2 years of treatment, these key events lead to a constitutive focal proliferative phenotype and a low incidence of renal tumours appearing late in life. Based on this research, the weight of evidence on genotoxicity, gender and mouse strain specificity, and the dose response and temporal relationships of chronic sustained non-neoplastic degenerative/regenerative tubular changes with renal neoplasms, the renal tumours observed in mice are considered irrelevant for humans. The safety margin relative to

the 25 mg/day dose of empagliflozin further mitigates uncertainties regarding the human relevance of the single-gender liability observed in the mouse. Aside from the expected pharmacology of SGLT-2 inhibition in clinical trials with empagliflozin, there is no evidence of safety risks for drug-related renal injury (biomarkers of glomerular or tubular damage, permanent or progressive reduction in renal function) or renal cancers.

Malignancy is a serious condition which may have serious complications (including due to the required treatment) and decrease the quality of life. Further characterisation of the risk will be provided from the ongoing PASS (1245-0097).

SVII.3.1.1.3 Characterisation of the risk

Paediatric T2DM indication (trial 1218-0091)

Urinary bladder and tract malignancies

No patients were identified with urinary bladder and tract malignancies in either treatment group (data on file, rmp-output-paediatric, Table 15.2.3.1: 1).

Renal malignancies

No patients were identified with renal malignancies in either treatment group (data on file, rmp-output-paediatric, Table 15.2.3.1: 1).

Indication CKD (trial 1245-0137)

Urinary bladder and tract malignancies

The percentage of patients with urinary bladder and tract malignancies was 0.2% in each treatment group. The incidence rate ratio and risk ratio showed no differences between both treatment groups. All events were serious and mainly required/prolonged hospitalisation or were serious due to other medical reasons. All patients in the placebo group and about half of the patients in the empagliflozin 10 mg group had recovered from the event at the time of database lock. Further details are summarised in the table below.

SVII.Table 15 Overview of patients with urinary bladder and tract malignancies (1245-00137) - TS

	Placebo	Empagliflozin 10 mg
Number of patients treated, N (%)	3305 (100.0)	3304 (100.0)
Patients with urinary bladder and tract malignancies, N (%)	5 (0.2)	7 (0.2)
Rate per 100 PY	0.08	0.12
95% CI	0.03, 0.19	0.05, 0.24
Incidence rate ratio[1] (95% CI)	-	1.40 (0.44, 4.40)
Incidence rate difference[1] (95% CI)	-	0.03 (−0.08, 0.14)
Risk ratio[1] (95% CI)	-	1.40 (0.44, 4.41)
Risk difference[1] (95% CI)	-	0.06 (−0.14, 0.27)
Urinary bladder and tract malignancies leading to discontinuation, N (%)	0	0
Seriousness[2], N (%)	5 (0.2)	7 (0.2)
Is life threatening	0	1 (<0.1)
Requires/prolongs hospitalisation	4 (0.1)	3 (0.1)
Other medically important serious event	1 (<0.1)	3 (0.1)
Outcome[3], N (%)		
Recovered/resolved	5 (0.2)	3 (0.1)
Not recovered/not resolved	0	4 (0.1)

Patients with urinary bladder and tract malignancies were identified using the following BIcMQ: 'Malignancies' – broad sub-search 14.1 'Urinary bladder malignancies' (MedDRA version 25.0).

[1] Respective active treatment vs. placebo.
[2] Only 1 reason for meeting the seriousness criterion could be selected.
[3] Each event is counted in the worst category observed, i.e. not recovered would not be a subset of fatal.
Data source: data on file, rmp-output-ckd, Tables 15.1.3.1: 1, 15.1.3.1: 2, 15.1.3.1: 4, 15.1.3.1: 7 'urinary bladder and tract malignancies'

Renal malignancies

The percentage of patients with renal malignancies was 0.2% in the placebo group and 0.3% in the empagliflozin 10 mg group. The incidence rate ratio and risk ratio showed no differences between both treatment groups. All events were serious and mainly required/prolonged hospitalisation or were serious due to other medical reasons. There was 1 fatal event in the empagliflozin 10 mg group. Further details are summarised in the table below.

SVII.Table 16 Overview of patients with renal malignancies (1245-0137) - TS

	Placebo	Empagliflozin 10 mg
Number of patients treated, N (%)	3305 (100.0)	3304 (100.0)
Patients with renal malignancies, N (%)	8 (0.2)	11 (0.3)
Rate per 100 PY	0.13	0.18
95% CI	0.06, 0.26	0.09, 0.32
Incidence rate ratio[1] (95% CI)	-	1.37 (0.55, 3.41)
Incidence rate difference[1] (95% CI)	-	0.05 (−0.09, 0.19)
Risk ratio[1] (95% CI)	-	1.38 (0.55, 3.42)
Risk difference[1] (95% CI)	-	0.09 (−0.17, 0.35)
Renal malignancies leading to discontinuation, N (%)	2 (0.1)	3 (0.1)
Seriousness[2], N (%)	8 (0.2)	11 (0.3)
Results in death	0	1 (<0.1)
Is life threatening	0	1 (<0.1)
Requires/prolongs hospitalisation	5 (0.2)	6 (0.2)
Other medically important serious event	4 (0.1)	3 (0.1)
Outcome[3], N (%)		
Recovered/resolved	4 (0.1)	5 (0.2)
Not recovered/not resolved	4 (0.1)	5 (0.2)
Fatal	0	1 (<0.1)

Patients with renal malignancies were identified using the following BIcMQ: 'Malignancies' – broad sub-search 14.2 'Renal malignancies' (MedDRA version 25.0).

[1] Respective active treatment vs. placebo.
[2] Only 1 reason for meeting the seriousness criterion could be selected.
[3] Each event is counted in the worst category observed, i.e. not recovered would not be a subset of fatal.
Data source: data on file, rmp-output-ckd, Tables 15.1.3.1: 1, 15.1.3.1: 2, 15.1.3.1: 4, 15.1.3.1: 7 'renal malignancies'

Indication HFpEF

Clinical trial data (SAF-HF4)

Urinary bladder and tract malignancies

The percentage of patients with urinary bladder and tract malignancies was low in both treatment groups. The incidence rate ratio and risk ratio showed no substantial differences between both treatment groups. The events mostly required/prolonged hospitalisation or were serious due to other medical reasons. The events were mainly of moderate or severe intensity with similar proportions in either treatment group. Most patients had not recovered from the event at the time of database lock. There was 1 fatal event in the empagliflozin 10 mg group. Further details are summarised in the table below.

Subgroup analyses

No clinically relevant difference in the frequency of urinary bladder and tract carcinogenicity between patients treated with empagliflozin and placebo was observed in any subgroup with

regard to gender, race, age, degree of renal impairment at baseline (eGFR), and diabetes mellitus status at baseline (data on file, SAF-HF4(HFpEF), Tables 4.1.9 to 4.1.13 'urinary bladder and tract malignancies').

SVII.Table 17 Overview of patients with urinary bladder and tract malignancies (SAF-HF4) - TS

	Placebo	Empagliflozin 10 mg
Number of patients treated, N (%)	3160 (100)	3175 (100)
Patients with urinary bladder and tract malignancies, N (%)	4 (0.1)	11 (0.3)
Rate per 100 PY	0.07	0.19
95% CI	0.02, 0.18	0.10, 0.35
Incidence rate ratio[1] (95% CI)	-	2.73 (0.87, 8.59)
Incidence rate difference[1] (95% CI)	-	0.12 (−0.01, 0.26)
Risk ratio[1] (95% CI)	-	2.74 (0.87, 8.58)
Risk difference[1] (95% CI)	-	0.22 (−0.02, 0.46)
Urinary bladder and tract malignancies leading to discontinuation, N (%)	1 (<0.1)	2 (0.1)
Seriousness[2], N (%)	4 (0.1)	11 (0.3)
Results in death	0	1 (<0.1)
Requires/prolongs hospitalisation	3 (0.1)	6 (0.2)
Other medically important serious event	2 (0.1)	9 (0.3)
Severity, N (%)		
Mild	1 (<0.1)	0
Moderate	2 (0.1)	7 (0.2)
Severe	1 (<0.1)	4 (0.1)
Outcome[3], N (%)		
Unknown	1 (<0.1)	2 (0.1)
Recovered/resolved	1 (<0.1)	2 (0.1)
Not recovered/resolved	2 (0.1)	6 (0.2)
Fatal	0	1 (<0.1)

Patients with urinary bladder and tract malignancies were identified using the following BIcMQ: 'Malignancies' – broad sub-search 14.1 'Urinary bladder malignancies' (MedDRA version 23.1).

[1] Respective active treatment vs. placebo.
[2] Patients can be counted in more than one seriousness category.
[3] Each of the outcomes could be individually assigned to an event, i.e. not recovered would not be a subset of fatal.
Data source: data on file, SAF-HF4(HFpEF), Tables 4.1.1, 4.1.2, 4.1.4, 4.1.5, 4.1.8 'urinary bladder and tract malignancies'

Renal malignancies

The percentage of patients with renal malignancies was low in both treatment groups. The incidence rate ratio and risk ratio showed no substantial differences between both treatment groups. The events either required/prolonged hospitalisation or were serious due to other medical reasons. No clear patter with regard to intensity or outcome of the event was discernible. Further details are summarised in the table below.

Subgroup analyses

No clinically relevant difference in the frequency of renal malignancies between patients treated with empagliflozin and placebo was observed in any subgroup with regard to gender, race, age, degree of renal impairment at baseline (eGFR), and diabetes mellitus status at baseline (data on file, SAF-HF4(HFpEF), Tables 4.1.9 to 4.1.13 'renal malignancies').

SVII.Table 18 Overview of patients with renal malignancies (SAF-HF4) - TS

	Placebo	Empagliflozin 10 mg
Number of patients treated, N (%)	3160 (100)	3175 (100)
Patients with renal malignancies, N (%)	6 (0.2)	5 (0.2)
Rate per 100 PY	0.11	0.09
95% CI	0.04, 0.23	0.03, 0.21
Incidence rate ratio[1] (95% CI)	-	0.83 (0.25, 2.71)
Incidence rate difference[1] (95% CI)	-	−0.02 (−0.13, 0.10)
Risk ratio[1] (95% CI)	-	0.83 (0.25, 2.71)
Risk difference[1] (95% CI)	-	−0.03 (−0.24, 0.17)
Renal malignancies leading to discontinuation, N (%)	0	0
Seriousness[2], N (%)	6 (0.2)	5 (0.2)
Requires/prolongs hospitalisation	3 (0.1)	4 (0.1)
Other medically important serious event	3 (0.1)	3 (0.1)
Severity, N (%)		
Mild	3 (0.1)	1 (<0.1)
Moderate	1 (<0.1)	1 (<0.1)
Severe	2 (0.1)	3 (0.1)
Outcome[3], N (%)		
Unknown	1 (<0.1)	1 (<0.1)
Recovered/resolved with sequelae	1 (<0.1)	0
Recovered/resolved	2 (0.1)	1 (<0.1)
Not recovered/resolved	2 (0.1)	3 (0.1)

Patients with renal malignancies were identified using the following BIcMQ: 'Malignancies' – broad sub-search 14.2 'Renal malignancies' (MedDRA version 23.1).

[1] Respective active treatment vs. placebo.
[2] Patients can be counted in more than one seriousness category.
[3] Each of the outcomes could be individually assigned to an event, i.e. not recovered would not be a subset of fatal.
Data source: data on file, SAF-HF4(HFpEF), Tables 4.1.1, 4.1.2, 4.1.4, 4.1.5, 4.1.8 'renal malignancies'

Indication HFrEF

Clinical trial data (SAF-HF5)

The percentage of patients with urinary tract carcinogenicity was low and comparable between both treatment groups (0.3% each). The incidence rate ratio and risk ratio showed no substantial differences between both treatment groups. The events either required/prolonged hospitalisation or were serious due to other medical reasons, with similar proportions between the treatment groups. Most events were of moderate or severe intensity with similar proportions in either treatment group. About half of the patients in each treatment group had recovered from the event at the time of database lock. There were no fatal events. Further details are summarised in SVII.Table 19.

Bladder cancer
The percentage of patients reported with bladder cancer was low (≤0.3%) and comparable between treatment groups. The incidence rate ratio and risk ratio for empagliflozin vs. placebo showed no substantial differences between both treatment groups. The events either required/prolonged hospitalisation or were serious due to other medical reasons, with similar proportions between the treatment groups. Most events were of moderate or severe intensity with similar proportions in either treatment group. About half of the patients in each treatment group had recovered from the event at the time of database lock. There were no fatal events (data on file, SAF-HF5(HFrEF), Tables 4.1.1, 4.1.2, 4.1.4, 4.1.5, 4.1.6, 4.1.8 'urinary tract carcinogenicity').

Renal cancer
The percentage of patients reported with renal cancer was low (≤0.1%) and comparable between treatment groups. The incidence rate ratio and risk ratio for empagliflozin vs. placebo showed no substantial differences between both treatment groups. The events either required/prolonged hospitalisation or were serious due to other medical reasons, with similar proportions between the treatment groups. Most events were of moderate or severe intensity with similar proportions in either treatment group. About half of the patients in each treatment group had recovered from the event at the time of database lock. There were no fatal events (data on file, SAF-HF5(HFrEF), Tables 4.1.1, 4.1.2, 4.1.4, 4.1.5, 4.1.6, 4.1.8 'urinary tract carcinogenicity').

Subgroup analyses
No clinically relevant difference in the frequency of urinary tract carcinogenicity between patients treated with empagliflozin and placebo was observed in any subgroup with regard to gender, race, age, degree of renal impairment at baseline (eGFR), and diabetes mellitus status at baseline (data on file, SAF-HF5(HFrEF), Tables 4.1.9 to 4.1.12 and Table 1.1.1 'urinary tract carcinogenicity').

SVII.Table 19 Overview of patients with urinary tract carcinogenicity (SAF-HF5) - TS

	Placebo	Empagliflozin 10 mg
Number of patients treated, N (%)	2019 (100.0)	2018 (100.0)
Urinary tract carcinogenicity		
Patients with urinary tract carcinogenicity, N (%)	6 (0.3)	7 (0.3)
Rate per 100 PY	0.26	0.30
95% CI	0.10, 0.57	0.12, 0.63
Incidence rate ratio[1] (95% CI)	-	1.16 (0.39, 3.44)
Incidence rate difference[1] (95% CI)	-	0.04 (-0.27, 0.35)
Risk ratio[1] (95% CI)	-	1.17 (0.39, 3.46)
Risk difference[1] (95% CI)	-	0.05 (-0.30, 0.40)
Urinary tract carcinogenicity leading to discontinuation, N (%)	0 (0.0)	2 (0.1)
Seriousness[2], N (%)	6 (0.3)	7 (0.3)
Requires/prolongs hospitalisation	3 (0.1)	5 (0.2)
Other medically important serious event	4 (0.2)	5 (0.2)
Severity, N (%)		
Mild	0 (0.0)	1 (<0.1)
Moderate	3 (0.1)	2 (0.1)
Severe	3 (0.1)	4 (0.2)
Outcome[3], N (%)		
Unknown	0 (0.0)	1 (<0.1)
Recovered/resolved	3 (0.1)	3 (0.1)
Not recovered/resolved	3 (0.1)	3 (0.1)
Bladder cancer		
Patients with bladder cancer, N (%)	6 (0.3)	4 (0.2)
Rate per 100 PY	0.26	0.17
95% CI	0.10, 0.57	0.05, 0.44
Renal cancer		
Patients with renal cancer, N (%)	0	3 (0.1)
Rate per 100 PY	--	0.13
95% CI	--	0.03, 0.38

Patients with bladder cancer were identified using the following BIcMQs: 'Malignancies' – broad sub-search 14.1 'Urinary bladder malignancies' and 'Malignancies' – broad sub-search 14.2 'Renal malignancies' (MedDRA version 23.0).

[1] Respective active treatment vs. placebo.

[2] Patients can be counted in more than one seriousness category.

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

Data source: data on file, SAF-HF5(HFrEF), Tables 4.1.1, 4.1.2, 4.1.4, 4.1.5, 4.1.8 'urinary tract carcinogenicity'; bladder and renal cancer_SAF-HF5+SAF-43 (R1331), Tables 20.1.1.1 and 20.1.1.2 'Urinary bladder and tract malignancies', 'renal malignancies'

Adult T2DM indication

Clinical trial data (SAF-43)

The percentage of patients reported with urinary tract carcinogenicity was low and comparable across treatment groups (0.2% each). The incidence rate ratio and risk ratio for empagliflozin 10/25 mg vs. placebo showed no substantial differences between the treatment groups. All of the events were serious and the majority required hospitalisation. There were 2 fatal events in the empagliflozin 10/25 mg group. The percentage of patients with urinary tract carcinogenicity events leading to treatment discontinuation was low and comparable across the treatment group (0.1% each). The reported urinary tract carcinogenicity events were mainly of moderate to severe intensity; most of the severe events occurred in the empagliflozin 10/25 mg group. No clear pattern towards outcome of the event was observed. Further details are summarised in the table below.

Bladder cancer

The percentage of patients reported with bladder cancer was low and comparable across treatment groups (≤0.1%). The incidence rate ratio and risk ratio for empagliflozin 10/25 mg vs. placebo showed no substantial differences between the treatment groups. All of the events were serious and the majority required hospitalisation. There were 2 fatal bladder cancer events in the empagliflozin 10/25 mg group. The reported events were mainly of moderate to severe intensity; most of the severe events occurred in the empagliflozin 10/25 mg group. No clear pattern towards outcome of the event was observed (data on file, SAF-43, Tables 31.4.1.1.1, 31.4.1.1.2, 31.4.1.1.3, 31.4.1.1.4, 31.4.1.1.14 'urinary tract carcinogenicity').

Renal cancer

The percentage of patients reported with renal cancer was low and comparable across treatment groups (≤0.1%). The incidence rate ratio and risk ratio for empagliflozin 10/25 mg vs. placebo showed no substantial differences between the treatment groups. All of the events were serious and the majority required hospitalisation. There were no fatal renal cancer events. The reported events were mainly of moderate to severe intensity; most of the severe events occurred in the empagliflozin 10/25 mg group. No clear pattern towards outcome of the event was observed (data on file, SAF-43, Tables 31.4.1.1.1, 31.4.1.1.2, 31.4.1.1.3, 31.4.1.1.4, 31.4.1.1.14 'urinary tract carcinogenicity').

Subgroup analyses

Subgroup analyses (gender, race, age, or degree of renal impairment at baseline [eGFR]) showed no clear trend towards any treatment group; however, the very low number of patients with urinary tract carcinogenicity makes a sound interpretation of these results difficult.

SVII.Table 20 Overview of patients with urinary tract carcinogenicity (SAF-43) - TS

	Placebo	Empagliflozin 10/25 mg
Number of patients treated, N (%)	4904 (100.0)	10 177 (100.0)
Urinary tract carcinogenicity		
Patients with urinary tract carcinogenicity, N (%)	9 (0.2)	23 (0.2)
Rate per 100 PY	0.11	0.14
95% CI	0.05, 0.22	0.09, 0.21
Incidence rate ratio[1] (95% CI)	-	1.12 (0.61, 2.04)
Incidence rate difference[1] (95% CI)	-	0.02 (-0.09, 0.13)
Risk ratio[1] (95% CI)	-	1.24 (0.57, 2.68)
Risk difference[1] (95% CI)	-	0.04 (-0.11, 0.20)
Urinary tract carcinogenicity leading to discontinuation, N (%)	4 (0.1)	11 (0.1)
Seriousness[2], N (%)	9 (0.2)	23 (0.2)
Fatal	0 (0.0)	2 (0.0)
Requiring hospitalisation	6 (0.1)	16 (0.2)
Prolonged hospitalisation	1 (0.0)	0 (0.0)
Other	3 (0.1)	6 (0.1)
Severity, N (%)		
Mild	0 (0.0)	0 (0.0)
Moderate	5 (0.1)	6 (0.1)
Severe	4 (0.1)	16 (0.2)
Outcome[3], N (%)		
Recovered	5 (0.1)	6 (0.1)
Not yet recovered	3 (0.1)	11 (0.1)
Sequelae	0 (0.0)	2 (0.0)
Fatal	0 (0.0)	2 (0.0)
Unknown	1 (0.0)	2 (0.0)
Bladder cancer		
Patients with bladder cancer, N (%)	4 (0.1)	13 (0.1)
Rate per 100 PY	0.05	0.08
95% CI	0.01, 0.13	0.04, 0.13
Renal cancer		
Patients with renal cancer, N (%)	5 (0.1)	10 (0.1)
Rate per 100 PY	0.06	0.06
95% CI	0.02, 0.15	0.03, 0.11

Patients with urinary tract carcinogenicity were identified using the BIcMQ 'Malignancies' – broad sub-search 14.1 'Urinary bladder and tract malignancies' and broad sub-search 14.2 'Renal malignancies' (MedDRA version 21.0). Information from the BI GSP was used to supplement the safety information about a case when available.

[1] Respective active treatment vs. placebo.

[2] Patients can be counted in more than one seriousness category.

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

Data source: Jardiance/Synjardy PBRER (reporting interval 18 Apr 2018 to 17 Apr 2019) [s00077934-01], Table 127; and data on file, bladder and renal cancer_SAF-HF5+SAF-43 (R1331), Tables 20.1.2.1 and 20.1.2.2 'Urinary bladder and tract malignancies', 'renal malignancies'

SVII.3.1.1.4 Risk factors and risk groups

Risk factors for bladder cancer are smoking, exposure to aromatic amines or aniline dyes, history of radiation treatment of the pelvis, chemotherapy with cyclophosphamide, and long-term indwelling urinary catheterisation.

Risk factors for renal cancer are smoking, obesity, hypertension, exposure to substances such as asbestos, cadmium, and benzene, and genetic hereditary diseases such as von Hippel-Lindau disease, and Birt-Hogg-Dube syndrome.

In addition to the known risk factors for bladder and renal cancers, the prevalence of comorbidities among patients (≥25 years) identified with various cancers was also estimated in a study in New Zealand [R20-2779]. 50 conditions that were diagnosed at least 5 years before a cancer diagnosis were identified from national routine hospital discharge databases (National Minimum Dataset). Locations of cancers were defined using ICD-Codes 10 based on New Zealand Cancer Register between 01 Jul 2006 and 30 Jun 2008. The top 3 conditions that were co-exiting when a bladder cancer was identified were: hypertension (primary) (15.6%), cardiac arrhythmia (10.4%), and diabetes (10.2%). Congestive heart failure accounted for 7.1%.

The top 3 prevalence of comorbidities among patients diagnosed with renal cancer were: hypertension (primary) (16.1%), diabetes (13.3%), and other metabolic disorders (11.2%). Congestive heart failure accounted for 4.7%.

SVII.3.1.1.5 Preventability

In general, there is no proven method of preventing malignancies but the risk of developing malignancies can be lowered through avoiding or managing the known risk factors (described in Section SVII.3.1.1.4).

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

Urinary tract cancer leads to long-term treatment (including hospitalisations) which may have severe complications itself and may have negative impact on the quality of life.

SVII.3.1.2 Important potential risk: Pancreatitis

SVII.3.1.2.1 Potential mechanisms

There is no known mechanism in which empagliflozin could cause drug-induced pancreatitis. The known pharmacodynamic effects of empagliflozin are not aetiological or risk factors for pancreatitis. There is no indication that treatment with empagliflozin may adversely affect the known aetiological or risk factors for pancreatitis.

SVII.3.1.2.2 Evidence source and strength of evidence

In clinical trials, there was no increase in the frequency of pancreatitis AEs with empagliflozin treatment compared to placebo. However, these results have limitations due to the relatively small sample size for capturing rare events.

Within post-authorisation experience, the information received does not provide strong evidence for a causal association between empagliflozin treatment and pancreatitis. Most of the case reports contain very limited information to allow for a causality assessment. In most of the remaining cases, concomitant conditions or drugs, or medical history provide an alternative aetiology of the event. In few cases, no alternative cause was reported among the concomitant or past diseases or drugs; rechallenge was not performed.

A PASS (1245-0201) is ongoing to further investigate this potential risk.

SVII.3.1.2.3 Characterisation of the risk

Paediatric T2DM indication (trial 1218-0091)
1 patient was reported with pancreatitis in the placebo group; there were no patients reported in the all empagliflozin group. The event was serious, of severe intensity, and the outcome was reported as recovered/resolved with sequelae (data on file, rmp-output-paediatric, Tables 15.2.3.1: 1, 15.2.3.1: 4, 15.2.3.1: 5, 15.2.3.1: 6).

Indication CKD (trial 1245-0137)
The percentages and IRs of patients with pancreatitis AEs were comparable between both treatment groups: placebo 0.2% (0.10/100 PY) and empagliflozin 10 mg 0.1% (0.05/100 PY). All events of pancreatitis were serious (only serious events were systematically collected for pancreatitis), mostly requiring/prolonging hospitalisation. There was 1 fatal event in the placebo group. Most patients had recovered from the events at the time of database lock. Further details are summarised in the table below.

SVII.Table 21 Overview of patients with pancreatitis (1245-0137) - TS

	Placebo	Empagliflozin 10 mg
Number of patients treated, N (%)	3305 (100.0)	3304 (100.0)
Patients with pancreatitis, N (%)	6 (0.2)	3 (0.1)
Rate per 100 PY	0.10	0.05
95% CI	0.04, 0.22	0.01, 0.14
Incidence rate ratio[1] (95% CI)	-	0.50 (0.12, 1.99)
Incidence rate difference[1] (95% CI)	-	−0.05 (−0.15, 0.05)
Risk ratio[1] (95% CI)	-	0.50 (0.13, 2.00)
Risk difference[1] (95% CI)	-	−0.09 (−0.27, 0.09)
Pancreatitis leading to discontinuation, N (%)	0	1 (<0.1)
Seriousness[2], N (%)	6 (0.2)	3 (0.1)
Results in death	1 (<0.1)	0
Requires/prolongs hospitalisation	4 (0.1)	3 (0.1)
Other medically important serious event	1 (<0.1)	0
Outcome[3], N (%)		
Unknown	1 (<0.1)	0
Recovered/resolved	4 (0.1)	2 (0.1)
Not recovered/not resolved	0	1 (<0.1)
Fatal	1 (<0.1)	0

Patients with pancreatitis were identified using the narrow SMQ 'Acute pancreatitis' and the MedDRA PT 'Pancreatitis chronic'(MedDRA version 25.0).

[1] Respective active treatment vs. placebo.
[2] Only 1 reason for meeting the seriousness criterion could be selected.
[3] Each event is counted in the worst category observed, i.e. not recovered would not be a subset of fatal.
Data source: data on file, rmp-output-ckd, Tables 15.1.3.1: 1, 15.1.3.1: 2, 15.1.3.1: 4, 15.1.3.1: 7 'pancreatitis'

Indication HFpEF

Clinical trial data (SAF-HF4)

The percentages and IRs of patients with pancreatitis AEs were higher in the placebo group compared to the empagliflozin 10 mg group: placebo 0.2% (0.12/100 PY) and empagliflozin 10 mg 0.1% (0.07/100 PY). All events of pancreatitis were serious, mostly requiring/prolonging hospitalisation. There was 1 fatal event in the placebo group. No clear pattern towards intensity of the event was observed. Most patients had recovered from the events at the time of database lock. Further details are summarised in the table below.

Subgroup analyses

No clinically relevant difference in the frequency of pancreatitis between patients treated with empagliflozin and placebo was observed in any subgroup with regard to gender, race, age, degree of renal impairment at baseline eGFR), and diabetes mellitus status at baseline; however, the low number of patients with pancreatitis needs to be taken into consideration (data on file, SAF-HF4(HFpEF), Tables 4.1.9 to 4.1.13 'pancreatitis').

SVII.Table 22 Overview of patients with pancreatitis (SAF-HF4) - TS

	Placebo	Empagliflozin 10 mg
Number of patients treated, N (%)	3160 (100)	3175 (100)
Patients with pancreatitis, N (%)	7 (0.2)	4 (0.1)
Rate per 100 PY	0.12	0.07
95% CI	0.05, 0.26	0.02, 0.18
Incidence rate ratio[1] (95% CI)	-	0.57 (0.17, 1.94)
Incidence rate difference[1] (95% CI)	-	−0.05 (−0.17, 0.06)
Risk ratio[1] (95% CI)	-	0.57 (0.17, 1.94)
Risk difference[1] (95% CI)	-	−0.10 (−0.30, 0.11)
Pancreatitis leading to discontinuation, N (%)	1 (<0.1)	1 (<0.1)
Seriousness[2], N (%)	7 (0.2)	4 (0.1)
Results in death	1 (<0.1	0
Requires/prolongs hospitalisation	6 (0.2)	4 (0.1)
Other medically important serious event	1 (<0.1)	0
Severity, N (%)		
Mild	2 (0.1)	1 (<0.1)
Moderate	3 (0.1)	1 (<0.1)
Severe	2 (0.1)	2 (0.1)
Outcome[3], N (%)		
Recovered/resolved	5 (0.2)	4 (0.1)
Not recovered/not resolved	1 (<0.1)	0
Fatal	1 (<0.1)	0

Patients with pancreatitis were identified using the narrow SMQ 'Acute pancreatitis' and the MedDRA PT 'Pancreatitis chronic'(MedDRA version 23.1).

[1] Respective active treatment vs. placebo.
[2] Patients can be counted in more than one seriousness category.
[3] Each of the outcomes could be individually assigned to an event, i.e. not recovered would not be a subset of fatal.
Data source: data on file, SAF-HF4(HFpEF), Tables 1.1, 4.1.2, 4.1.4, 4.1.5, 4.1.8 'pancreatitis'

Indication HFrEF

Clinical trial data (SAF-HF5)

The percentages and IRs of patients with pancreatitis AEs were higher in the placebo group compared to the empagliflozin 10 mg group: placebo 0.2% (0.17/100 PY) and empagliflozin 10 mg 0.1% (0.09/100 PY). All events of pancreatitis were serious, all but one requiring/prolonging hospitalisation with similar frequencies between both treatment groups. There was 1 fatal event. No clear pattern towards intensity of the event was observed. All but 1 patient had recovered from the events at the time of database lock. Further details are summarised in the table below.

Subgroup analyses

No clinically relevant difference in the frequency of pancreatitis between patients treated with empagliflozin and placebo was observed in any subgroup with regard to gender, race, age, degree of renal impairment at baseline eGFR), and diabetes mellitus status at baseline; however, the low number of patients with pancreatitis needs to be taken into consideration (data on file, SAF-HF5(HFrEF), Tables 4.1.9 to 4.1.12 and Table 1.1.1 'pancreatitis').

SVII.Table 23 Overview of patients with pancreatitis (SAF-HF5) - TS

	Placebo	**Empagliflozin 10 mg**
Number of patients treated, N (%)	2019 (100.0)	2018 (100.0)
Patients with pancreatitis, N (%)	4 (0.2)	2 (0.1)
Rate per 100 PY	0.17	0.09
95% CI	0.05, 0.45	0.01, 0.31
Incidence rate ratio[1] (95% CI)	-	0.50 (0.09, 2.71)
Incidence rate difference[1] (95% CI)	-	−0.09 (−0.30, 0.12)
Risk ratio[1] (95% CI)	-	0.50 (0.09, 2.73)
Risk difference[1] (95% CI)	-	−0.10 (−0.34, 0.14)
Pancreatitis leading to discontinuation, N (%)	0 (0.0)	1 (<0.1)
Seriousness[2], N (%)	4 (0.2)	2 (0.1)
Results in death	0 (0.0)	1 (<0.1)
Requires/prolongs hospitalisation	4 (0.2)	2 (0.1)
Severity, N (%)		
Mild	2 (0.1)	0 (0.0)
Moderate	0 (0.0)	1 (<0.1)
Severe	2 (0.1)	1 (<0.1)
Outcome[3], N (%)		
Recovered/resolved	4 (0.2)	1 (<0.1)
Fatal	0 (0.0)	1 (<0.1)

Patients with pancreatitis were identified using the narrow SMQ 'Acute pancreatitis' and the MedDRA PT 'Pancreatitis chronic'(MedDRA version 23.0).

[1] Respective active treatment vs. placebo.
[2] Patients can be counted in more than one seriousness category.
[3] Each of the outcomes could be individually assigned to an event, i.e. not recovered would not be a subset of fatal.
Data source: data on file, SAF-HF5(HFrEF), Tables 4.1.1, 4.1.2, 4.1.4, 4.1.5, 4.1.8 'pancreatitis'

Adult T2DM indication

Clinical trial data (SAF-43)

The frequencies and IRs of patients with pancreatitis AEs were higher in the placebo group compared to the empagliflozin groups: placebo 0.2% (0.14/100 PY) and empagliflozin 10/25 mg 0.1% (0.09/100 PY). The events of pancreatitis were mainly reported as serious (nearly all of them requiring hospitalisation) with similar frequencies across treatment groups; there were no fatal events. The percentage of patients with pancreatitis leading to discontinuation

was low (≤0.1%). No clear pattern towards intensity of the event was observed. The majority of patients had recovered from the events at the time of database lock. Diagnostic criteria (i.e. laboratory values, clinical symptoms, imaging results) were not consistently provided. Further details are summarised in the table below.

Subgroup analyses
Subgroup analyses (gender, race, age, or degree of renal impairment at baseline [eGFR]) showed no clear trend towards any treatment group; however, the very low number of patients with pancreatitis makes a sound interpretation of these results difficult.

SVII.Table 24 Overview of patients with pancreatitis (SAF-43) - TS

	Placebo	**Empagliflozin 10/25 mg**
Number of patients treated, N (%)	4904 (100.0)	10 177 (100.0)
Patients with pancreatitis, N (%)	11 (0.2)	15 (0.1)
Rate per 100 PY	0.14	0.09
95% CI	0.07, 0.25	0.05, 0.15
Incidence rate ratio[1] (95% CI)	-	0.76 (0.41,1.42)
Incidence rate difference[1] (95% CI)	-	-0.05 (-0.15,0.06)
Risk ratio[1] (95% CI)	-	0.65 (0.29, 1.45)
Risk difference[1] (95% CI)	-	-0.08 (-0.23, 0.07)
Pancreatitis leading to discontinuation, N (%)	1 (0.0)	7 (0.1)
Seriousness[2], N (%)	10 (0.2)	13 (0.1)
Requiring hospitalisation	10 (0.2)	12 (0.1)
Other	0 (0.0)	1 (0.0)
Severity, N (%)		
Mild	2 (0.0)	1 (0.0)
Moderate	1 (0.0)	6 (0.1)
Severe	8 (0.2)	8 (0.1)
Outcome[3], N (%)		
Recovered	11 (0.2)	13 (0.1)
Not yet recovered	0 (0.0)	1 (0.0)
Unknown	0 (0.0)	1 (0.0)

Patients with pancreatitis were identified using the narrow SMQ 'Acute pancreatitis' (MedDRA version 21.0).
[1] Respective active treatment vs. placebo.
[2] Patients can be counted in more than one seriousness category.
[3] Each of the outcomes could be individually assigned to an event, i.e. not recovered would not be a subset of fatal.
Data source: Jardiance/Synjardy PBRER (reporting interval 18 Apr 2018 to 17 Apr 2019) [s00077934-01], Table 159

SVII.3.1.2.4 Risk factors and risk groups

Patients with T2DM have an increased risk of pancreatitis. Further, obesity, history of alcohol use, history of smoking, higher comorbidity index, hypertriglyceridemia, 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 hypertriglyceridemia 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 hypertriglyceridemia were 1.71% vs. 0.95% ($p<0.0001$) [R10-5391].

SVII.3.1.2.5 Preventability

The prevention of pancreatitis includes correction of the known risk factors – control of diabetes, cessation of alcohol use and smoking, correction of the hypertriglyceridemia, and management of gall bladder diseases.

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

Pancreatitis is a potentially serious and life-threatening disease.

SVII.3.1.2.7 Public health impact

Not applicable.

SVII.3.2 Presentation of the missing information

There is no missing information for Jardiance.

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ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ALI	Acute liver injury
ALI1	Acute liver injury in patients without predisposing conditions
ALI2	Acute liver injury in patients with and without predisposing conditions
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim customised MedDRA query
CANVAS	Study acronym; Canagliflozin Cardiovascular Assessment Study
CD	Cluster of differentiation
CI	Confidence interval
CKD	Chronic kidney disease
CREDENCE	Study acronym; Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation
CV	Cardiovascular
CVOT	Cardiovascular outcome trial
DAPA-CKD	Study acronym; Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
DECLARE-TIMI 58	Study acronym; Dapagliflozin Effect on CardiovascuLAR Events
DILI	Drug-induced liver injury
DINAMO	Study acronym; DIabetes study of liNAgliptin and eMpagliflozin in children and adOlescents
DKA	Diabetic ketoacidosis
DLP	Datalock point
DPP-4	Dipeptidyl peptidase 4
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
Empa	Empagliflozin
EMPA-KIDNEY	Study acronym; The Study of Heart and Kidney Protection With Empagliflozin

EMPA-REG OUTCOME	Study acronym; EMPAgliflozin Removal of Excess of Glucose OUTCOME trial
EMPRISE	Study acronym; Empagliflozin Comparative Effectiveness and Safety
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GLP-1	Glucagon-like peptide-1
GLP-1a	Glucagon-like peptide-1 agonist
GLP-1RA	Glucagon-like peptide-1 receptor agonist
GSP	Global Safety Platform
GVP	Good Pharmacovigilance Practice
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HIRD	Health Insurance Responsibility Disclosure
HR	Hazard ratio
IC	Intermittent claudication
ICD	International Classification of Diseases
IR	Incidence rate
IRR	Incidence rate ratio
ITT	Intention-to-treat
LLA	Lower limb amputation
MedDRA	Medical Dictionary for Regulatory Activities
NC	Not calculated
NIS	Non-interventional study
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
PI	Product information
PT	Preferred term
PY	Patient-years
RMP	Risk Management Plan
SAE	Serious adverse event

SAF	Safety grouping
SD	Standard deviation
SGLT-2	Sodium-dependent glucose co-transporter 2
SMQ	Standardised MedDRA query
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
TS	Treated set
UK	United Kingdom
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection
vs.	Versus

MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

SVIII.Table 1 Summary of safety concerns

Important identified risks	None
Important potential risks	Urinary tract carcinogenicity Pancreatitis
Missing information	None

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 (T2DM indication) for:

- Pancreatitis

Other forms of routine pharmacovigilance activities for:
None.

PART III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Part III.2.1 PASS 1245-0097 summary

Study short name and title
1245-0097 - Post-authorisation safety study to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with T2DM: a multi-database European study

Rationale and study objectives
To evaluate the risk of renal and bladder cancer in empagliflozin-treated patients, compared to users of other antidiabetic treatment

Study design
Observational, comparative, cohort safety study

Study population
Adult patients with T2DM

Milestones
Final report, 30 Sep 2023

PART III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

PIII.Table 1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
PASS 1245-0097 Post-authorisation safety study to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with T2DM: a multi-database European study Ongoing	To evaluate the risk of renal and bladder cancer in empagliflozin-treated patients, compared to users of other antidiabetic treatment.	Urinary tract carcinogenicity	Final report	30 Sep 2023

PART III.4 REFERENCES

Not applicable.

ABBREVIATIONS

PASS	Post-Authorisation Safety Study
T2DM	Type 2 diabetes mellitus

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 empagliflozin.

PART V RISK MINIMISATION MEASURES

RISK MINIMISATION PLAN

PART V.1 ROUTINE RISK MINIMISATION MEASURES

PV.Table 1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
None	
Important potential risks	
Urinary tract carcinogenicity	*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* Empagliflozin is available as prescription only medicine.
Pancreatitis	*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* Empagliflozin is available as prescription only medicine.
Missing information	
None	

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.

PART V.3 SUMMARY OF RISK MINIMISATION MEASURES

PV.Table 2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None		
Important potential risks		
Urinary tract carcinogenicity	*Routine risk minimisation measures* Prescription only medicine *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* None *Additional pharmacovigilance activities* PASS 1245-0097 (final report 30 Sep 2023)
Pancreatitis	*Routine risk minimisation measures* Prescription only medicine *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form to capture data on patients with pancreatitis. *Additional pharmacovigilance activities* None
Missing information		
None		

PART V.4 REFERENCES

Not applicable.

ABBREVIATIONS

AE	Adverse event
PASS	Post-Authorisation Safety Study
PL	Package Leaflet
SmPC	Summary of Product Characteristics

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR JARDIANCE (EMPAGLIFLOZIN)

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

Jardiance's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Jardiance should be used.

This summary of the RMP for Jardiance should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 Jardiance's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Jardiance is authorised for the treatment of adults and children aged 10 years and above

- With insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.

Jardiance is authorised for the treatment of adults

- With symptomatic chronic heart failure independent of left ventricular ejection fraction.
- With chronic kidney disease

See SmPC for full indication. It contains empagliflozin as the active substance and it is given by oral administration.

Further information about the evaluation of Jardiance's benefits can be found in Jardiance's EPAR, including in its plain-language summary, 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 Jardiance, together with measures to minimise such risks and the proposed studies for learning more about Jardiance's risks, are outlined below.

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

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

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

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including 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 Jardiance is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Jardiance 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 Jardiance. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	None
Important potential risks	Urinary tract carcinogenicity Pancreatitis
Missing information	None

II.B Summary of important risks

There are no important identified risks or missing information for Jardiance.

Urinary tract carcinogenicity	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing experience with use of SGLT-2 inhibitors
Risk factors and risk groups	Risk factors for bladder cancer: smoking, exposure to aromatic amines or aniline dyes, history of radiation treatment of the pelvis, chemotherapy with cyclophosphamide, and long-term indwelling urinary catheterisation Risk factors for renal cancer: smoking, obesity, hypertension, exposure to substances such as asbestos, cadmium, and benzene, and genetic hereditary diseases such as von Hippel-Lindau disease, and Birt-Hogg-Dube syndrome
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine

	Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS 1245-0097 See Section II.C of this summary for an overview of the post-authorisation development plan.
Pancreatitis	
Evidence for linking the risk to the medicine	Clinical trial and post-marketing data with use of empagliflozin In clinical trials, there was no increase in the frequency of pancreatitis AEs with empagliflozin treatment compared to placebo. However, these results are limited due to the small sample size for capturing rare events. Post-marketing experience does not provide strong evidence for a causal association between empagliflozin treatment and pancreatitis.
Risk factors and risk groups	T2DM, obesity, alcohol abuse, smoking, higher comorbidity index, hypertriglyceridaemia, any history of gallbladder disease
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None

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 obligation of Jardiance.

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

PASS 1245-0097
Purpose of the study: To evaluate the risk of renal and bladder cancer in empagliflozin-treated patients, compared to users of other antidiabetic treatment

ABBREVIATIONS

AE	Adverse event
EMA	European Medicines Agency
EPAR	European Public Assessment Report
PASS	Post-Authorisation Safety Study
PL	Package leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan

SGLT-2	Sodium-dependent glucose co-transporter 2
SmPC	Summary of Product Characteristics
T2DM	Type 2 diabetes mellitus

PART VII APPENDICES

APPENDIX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Appendix - Table of Contents

Questionnaire: Pancreatitis Questionnaire - V 10.0

Questionnaire questions (Q:)

Context in LSMV = Questionnaire

Question ID	Questionnaire Name	Question
Q:PAN01	Pancreatitis Questionnaire	Does the patient have a prior history of pancreatitis, elevated amylase or lipase?
Q:PAN02	Pancreatitis Questionnaire	Does the patient have a history of gallstones?
Q:PAN03	Pancreatitis Questionnaire	Does the patient have hypertriglyceridemia?
Q:PAN04	Pancreatitis Questionnaire	If the patient have hypertriglyceridemia: What was the triglyceride level at onset of symptoms?
Q:PAN05	Pancreatitis Questionnaire	If the patient have hypertriglyceridemia: Other relevant information?
Q:PAN06	Pancreatitis Questionnaire	Does the patient have other gastrointestinal symptoms/diseases in his/her medical history?
Q:PAN07	Pancreatitis Questionnaire	Does the patient drink alcohol?
Q:PAN08	Pancreatitis Questionnaire	If the patient drinks alcohol: How many years?
Q:PAN09	Pancreatitis Questionnaire	If the patient drinks alcohol: Weekly alcohol intake (e.g., Wine, beer, 'hard' liquor)
Q:PAN10	Pancreatitis Questionnaire	If the patient drinks alcohol: Amount per week (ml)
Q:PAN11	Pancreatitis Questionnaire	Current or past history of alcohol use disorder or binge drinking? If yes, please specify
Q:PAN12	Pancreatitis Questionnaire	Did event occur after an episode of heavy drinking and/or eating?

Questionnaire: Pancreatitis Questionnaire - V 10.0

Q:PAN13	Pancreatitis Questionnaire	What symptoms did the patient have?
		- Abdominal Pain [No; Yes]
		  - Location [epigastric; right upper quadrant; other (please specify)]
		  - Character: (e.g., sharp, dull,burning)
		- Nausea [No; Yes]
		- Vomiting [No; Yes]
		- Other symptoms [No; Yes, please specify]

Q:PAN14	Pancreatitis Questionnaire	Laboratory results [Date; Value (U/L); Reference Range (upper and lower limits of normal)] - Amylase baseline - Amylase maximal value (during event) - Amylase follow-up - Lipase baseline - Lipase maximal value (during event) - Lipase follow-up - ALT/AST
Q:PAN15	Pancreatitis Questionnaire	Laboratory results [Date; Value (U/L); Reference Range (upper and lower limits of normal)] - Leucocyte count - CRP - Trypsinogen - Bilirubin - Alkaline phosphatase - Sodium/potassium/chloride - Blood urea/creatitine - Peritoneal lavage results - Other (please specify)

Questionnaire: Pancreatitis Questionnaire - V 10.0

Q:PAN16	Pancreatitis Questionnaire	Imaging results [Date; Result] - Abdominal sonogram - Abdominal CT scan - Magnetic Resonance Imaging (abdomen, pancreas, etc.) - Chest X-ray - Abdominal X-ray - Other (please specify)

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

There are no proposed additional risk minimisation activities for empagliflozin.