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ORIGINAL RESEARCH ARTICLE

Safety Profile of Dapagliflozin for Type 2 Diabetes: Pooled Analysis of Clinical Studies for Overall Safety and Rare Events

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Abstract

Background Dapagliflozin reduces hyperglycaemia in patients with type 2 diabetes mellitus (T2DM) by increasing urinary glucose excretion.

Objectives This study determined the overall safety profile of dapagliflozin in T2DM.

Methods Safety of dapagliflozin in pooled analyses of phase IIb/III studies was evaluated. Patients received comparator or dapagliflozin as monotherapy, add-on to antidiabetic therapy, or as initial combination with metformin. Proportions of patients with adverse events (AEs) and prespecified parameters related to previous clinical observations and dapagliflozin's action were assessed. The principal analysis used data from 12 placebo-controlled studies. Rare events were assessed across phase IIb/III studies, including special populations, comparator-controlled trials and ongoing long-term extensions.

Results In placebo-controlled studies, hypoglycaemia was more common with dapagliflozin (11.8 %) than placebo (7.0 %), with imbalance driven by add-on of dapagliflozin to sulfonylurea or insulin. Urinary tract infections (4.8 vs 3.7 %), vulvovaginitis/balanitis and related infections (5.1 vs 0.9 %), and non-serious volume-related events (0.8 vs 0.4 %) occurred more often with dapagliflozin than placebo. No substantial AEs were seen on electrolytes or renal function. Pyelonephritis was rare and balanced among treatments; there were no imbalances in fractures or liver test elevations. Overall incidence of malignancies was balanced between groups. The incidence rate ratios of malignancy in certain organ systems were slightly lower for dapagliflozin (renal tract, female reproductive) and in others were slightly lower for control (breast, prostate, bladder). Most AEs associated with dapagliflozin were mild/moderate and related to the mechanism of action.

Conclusion Dapagliflozin has a favourable and predictable tolerability profile, with reported events related to its mechanism of action.

Key Points

Dapagliflozin has a favourable and predictable tolerability profile, with reported events related to its mechanism of action

Low rates of hypoglycaemia, long-term safety data and few discontinuations, suggest that dapagliflozin may be used for the long-term treatment of T2DM in a broad spectrum of patients

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1 Introduction

Dapagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, is a novel therapy for the treatment of type 2 diabetes mellitus (T2DM) that lowers plasma glucose by inhibiting renal glucose reabsorption independently of insulin secretion or action.

A comprehensive, phase 2b/3 global clinical development programme involving a broad T2DM population in studies lasting up to 102 weeks found that once-daily, 5 or 10 mg oral dapagliflozin significantly reduced blood glucose levels and was well tolerated as monotherapy [1, 2] and in combination with various antidiabetic agents (metformin [3, 4], a sulfonylurea [5], insulin [6] or a thiazolidinedione [7]). In head-to-head trials, dapagliflozin demonstrated similar antihyperglycaemic efficacy to glipizide [4] and metformin [8]. By its mechanism of action, dapagliflozin reduces fasting and postprandial glucose concentrations resulting in long-term reductions in haemoglobin A1c (HbA_{1c}) [3]. The efficacy of dapagliflozin in reducing HbA_{1c} is similar to that of other antidiabetic agents [4, 8].

Furthermore, the combination of dapagliflozin with numerous commonly used drugs known to be enzyme inducers/inhibitors has been assessed in pharmacokinetic studies [9–11]. No clinically significant pharmacokinetic alterations were noted for either dapagliflozin or the investigated drugs.

Dapagliflozin did not affect QT interval or heart rate at supratherapeutic doses (20 and 150 mg) in healthy males [12], and decreased blood pressure (BP) in the dapagliflozin development programme [1, 3–6, 13, 14]. A separate, independently adjudicated meta-analysis suggests that dapagliflozin does not pose a cardiovascular (CV) risk versus comparators, as the hazard ratio for CV death, stroke, myocardial infarction, stroke and hospitalization for unstable angina was 0.82 (95 % confidence interval [CI] 0.58, 1.15) [15].

Whilst these data show a favourable/manageable adverse event (AE) profile, a pooled analysis of phase IIb/III clinical trials was conducted to increase the precision of risk estimate for identified side effects, to increase sensitivity to capture signals that might not be detected in individual studies and to develop a comprehensive understanding of the safety profile of this first-in-class antidiabetic agent.

In addition to typical safety parameters common to all developmental programmes, analyses were focused on safety concerns related to the site and mechanism of dapagliflozin action: hypoglycaemia, a common concern for all antidiabetic agents; renal function in a population at risk for nephropathy; events potentially related to chronic glucosuria, such as urinary and genital infections; and concerns related to mild osmotic diuresis, including dehydration or volume depletion, and its effects on electrolyte balance and bone health. Potential rare events were also captured.

2 Methods

2.1 Pooled Populations

The data cutoff date for all studies occurred on or before June 25, 2010. Most studies assessed dapagliflozin doses of 2.5, 5 and 10 mg. One phase III study had a 1 mg dosing arm; this cohort was not included in the analysis. The principal population analysed comprised 12 phase IIb/III clinical trials ranging from 12 to 24 weeks in duration and involving >4,000 patients (Fig. 1). This population was used to assess dapagliflozin safety as it had the fewest missing observations and used a single comparator. Of these, five trials had double-blind, long-term extensions (of up to 102 weeks), which were used to assess potential safety signals that might manifest with longer drug exposure. Supplementary analyses of the placebo-controlled studies were conducted for patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] $\geq$30 and <60 mL/min/1.73 m^2) and for patients aged $\geq$65 or $\geq$75 years.

To increase sensitivity and capture rarer events, in addition to the 12 placebo-controlled trials, data from an active comparator trial and a trial in a special population (moderate renal impairment) were also included (14 studies total) [1, 3–6, 8, 13, 14, 16–20]. This broader population was used to analyse deaths, serious AEs (such as serious renal and volume-related events), kidney infections, urinary stones, fractures and abnormal liver function.

As the clinical programme matured and more data became available, a further update to capture malignancy data in patients with any exposure to dapagliflozin or comparator was performed to include data up to July 15, 2011. In addition to the studies noted above, this included five studies on-going at the time of the initial analysis [21–23], and studies D1690C00018 NCT01031680 and D1690C00019 NCT01042977 (data on file) (19 studies total) (Electronic Supplementary Material 1).

2.2 Safety Data Collection

- In all studies, AEs, standard clinical laboratory tests and vital signs were recorded, as previously described [1, 3–6, 13, 14, 16, 17]. As glucose is invariably present in urine due to the mechanism of action of dapagliflozin, urine glucose levels were excluded from analyses

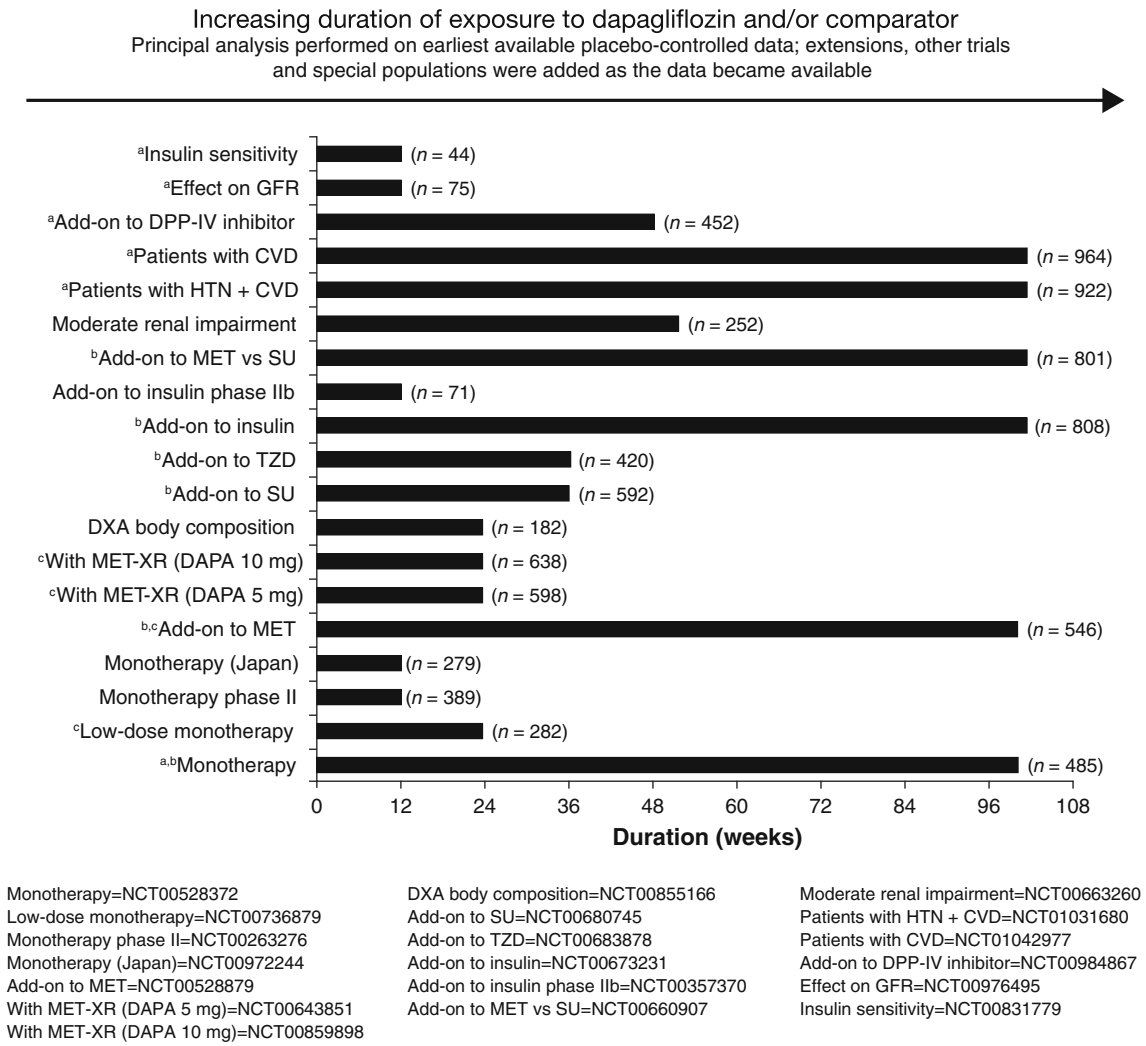

Fig. 1 Key populations for safety assessments. [a] Studies were ongoing at the time of the primary analysis. [b] Extension periods were ongoing at the time of the primary analysis. [c] Uric acid assessed. *CVD* cardiovascular disease, *DPP-IV* dipeptidyl peptidase IV, *DXA* dual-energy X-ray absorptiometry, *GFR* glomerular filtration rate, *HTN* hypertension, *MET* metformin, *MET-XR* metformin extended release, *SU* sulfonylurea, *TZD* thiazolidinedione

as a safety parameter. Investigators determined AE severity as:

- Mild—awareness of the events but easily tolerated.
- Moderate—discomfort enough to cause interference with usual activity.
- Severe—inability to carry out usual activity.
- Very severe—debilitating, significantly incapacitating despite treatment.

Investigators were asked to report AEs as related when believed that reasonable causal relationship to the study drug administration existed. Serious AEs were reported based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) definition.

2.2.1 Events of Clinical Interest

Events of clinical interest were prespecified and analysed separately. Hypoglycaemic events were reported on special case report forms (CRFs) and categorized as major, minor or other as previously described [6]. These events were identified based on nonclinical and clinical findings, as well as putative considerations based on the mechanism of action of dapagliflozin, T2DM disease and antidiabetic treatments.

The following AEs were prespecified for specific review and analysis and collected in standard CRFs: hypotension/dehydration/hypovolaemia (volume depletion), urinary stones, thromboembolic events, fracture and renal impairment/failure. AEs of genital infections (not including helminthic infections or sexually transmitted diseases) and

urinary tract infections (UTIs), including kidney infections, were collected on special CRFs. As each of these events could be reported and coded across multiple Medical Dictionary for Regulatory Activities (MedDRA®) preferred terms (PTs), customized MedDRA® queries based on predefined lists of PTs were developed for these events or standardized MedDRA® queries were used. MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the ICH. MedDRA® trademark is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) on behalf of ICH. Signs and symptoms of genital infection or UTI were actively solicited at each study visit, evaluated and related to PTs resulting in a clinical diagnosis.

Data on hepatic clinical events and tests were collected on special CRFs. Hepatic events were assessed in detail by an independent, blinded adjudication committee to evaluate the potential for drug-induced liver injury. CV events were similarly assessed and have been reported elsewhere.

PTs (AEs) included in the standard MedDRA® query for 'malignant or unspecified tumours' were used to identify possible cancer events. Standardized questionnaires were used for breast, bladder, prostate and thyroid events that were reported as AEs and coded to relevant PTs. All suspected 'cancers' were reviewed for confirmation of benign or malignant status.

2.2.2 *Safety Data Analysis*

Unless otherwise indicated, analyses were performed for all patients who received at least one dose of study medication during the double-blind treatment period.

Analyses performed on the placebo-controlled pools included data after rescue therapy initiation. Analysis of hypoglycaemic events was performed excluding data after initiation of rescue treatment for selected safety variables. For all analyses and summaries of safety measures, missing values were not imputed.

The difference in incidence rates of malignant and unspecified tumours was calculated using Cochran–Mantel–Haenszel exposure weights, stratified by study, with CIs based on an exact method.

3 Results

3.1 Patients and Exposure

Patient demographics were balanced across treatment groups in the placebo-controlled studies used for the principal analysis (Table 1). Most patients (≈90 %) were overweight (body mass index ≥25 kg/m^2). The mean diabetes duration ranged from 5.3 to 6.7 years. Mean baseline HbA_{1c} ranged from 8.1 to 8.4 % for all groups, although 24–28 % of patients had baseline values ≥9 %. Approximately 50 % of patients were treated with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, 20 % received thiazides and 4 % were taking loop diuretics. Mean baseline HbA_{1c} in dapagliflozin monotherapy studies ranged from 7.8 to 7.9 % for placebo and dapagliflozin groups, respectively, mean T2DM duration was 0.5 years for placebo and 0.4 years for dapagliflozin arms, and 21–25 % of patients had a history of T2DM ranging from 3 to 10 years. Mean T2DM duration in studies of dapagliflozin plus metformin was 6.0 years for dapagliflozin groups and 5.7 years for placebo groups and ≈48 % of patients had a history of T2DM ranging from 3 to 10 years. Patients receiving dapagliflozin as initial combination with metformin had a higher baseline HbA_{1c} (≈9.1 %) [8]. Patients in the phase III add-on to insulin study had a longer mean T2DM duration (13.6 years) and slightly higher baseline HbA_{1c} (7.7 and 7.6 % for placebo and dapagliflozin groups, respectively). Demographics across the different pooled populations were consistent (Electronic Supplementary Material 2).

The placebo-controlled pool, used for the principal analyses, comprised 3,291 patients who received dapagliflozin. Most (n = 2,481) were exposed for 6 months, 1,769 were exposed for 12 months, 1,017 for 18 months and 429 for 24 months. In the broader 14-studies pool, 4,287 patients received dapagliflozin compared with 1,941 patients who received control. In this pool, cumulative exposure to dapagliflozin was 4,009 patient-years (3,333 were exposed for 6 months, >50 % [n = 2,232] were exposed for 12 months, 1,317 for 18 months, and 441 for 24 months) while cumulative exposure to control was 1,681.9 patient-years. The 19-studies pool comprised 5,501 patients who received dapagliflozin and 3,184 patients who received control. Compared with the 14-studies pool, the 19-studies pool provided ∼46 % additional patient-years of exposure for dapagliflozin and 90 % for control.

3.2 Adverse Event Summary

In the placebo-controlled pool, most events (>90 %) were mild to moderate in intensity, and there was no apparent relationship between dapagliflozin dose and AE incidence. The proportion of patients reporting ≥1 AE was similar between dapagliflozin groups and higher for dapagliflozin (61.7 %) versus placebo (56.9 %) (Table 2). Treatment-related AEs were reported in 17.3 % of the dapagliflozin group, which included patients receiving 20 and 50 mg doses, compared with 13.3 % of the placebo group. Frequently reported adverse drug reactions in the dapagliflozin 10 mg group were hypoglycaemia, genital infections,

Table 1 Baseline characteristics for patients in the placebo-controlled 24-week pool (principal analysis)

	Placebo	Dapagliflozin			
	$n = 1,393$	2.5 mg $n = 814$	5 mg $n = 1,145$	10 mg $n = 1,193$	Total[a] $n = 3,291$
Age, years	55.3 ± 10.5	57.0 ± 10.6	55.4 ± 10.4	55.1 ± 10.1	55.6 ± 10.2
Male	716 (51.4)	414 (50.9)	564 (49.3)	595 (49.9)	1,643 (49.9)
Female	667 (48.6)	400 (49.1)	581 (50.7)	598 (50.1)	1,648 (50.1)
Race					
White	1,129 (81.0)	653 (80.2)	907 (79.2)	976 (81.8)	2,658 (80.8)
Black	38 (2.7)	15 (1.8)	33 (2.9)	35 (2.9)	94 (2.9)
Asian	201 (14.4)	127 (15.8)	181 (15.9)	152 (12.7)	463 (14.1)
Other[b]	25 (1.8)	19 (2.3)	24 (2.1)	30 (2.5)	76 (2.3)
Weight, kg	87.4 ± 19.5	86.1 ± 19.5	86.0 ± 19.0	88.0 ± 19.4	87.0 ± 19.3
Duration of type 2 diabetes, years	5.3 ± 6.4	6.7 ± 6.9	5.7 ± 6.6	6.2 ± 6.7	6.1 ± 6.7
HbA_{1c}	8.4 ± 1.2	8.1 ± 0.9	8.4 ± 1.1	8.3 ± 1.0	8.3 ± 1.0
Fasting plasma glucose, mmol/L	9.6 ± 2.9	9.2 ± 2.7	9.7 ± 2.9	9.4 ± 2.7	9.4 ± 2.7
Fasting c-peptide, nmol/L	1.1 ± 0.6	1.2 ± 0.6	1.1 ± 0.5	1.1 ± 0.6	1.1 ± 0.6
Seated systolic blood pressure, mmHg	$n = 1,320$	$n = 754$	$n = 1,087$	$n = 1,127$	$n = 2,974$
	130.0 ± 15.4	131.9 ± 17.0	129.0 ± 15.8	130.4 ± 16.2	130.3 ± 16.3
Seated diastolic blood pressure, mmHg	$n = 1,320$	$n = 754$	$n = 1,087$	$n = 1,127$	$n = 2,974$
	79.8 ± 8.7	79.6 ± 9.3	79.1 ± 9.0	79.2 ± 9.1	79.3 ± 9.1

Data are mean ± standard deviation or *n* (%). This table includes all treated patients. Percentages reported are based on the total number of patients in each treatment group

[a] Total includes dapagliflozin 20-mg and 50-mg doses

[b] Other includes patients with reported race of American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander or other

Table 2 Adverse event and hepatic laboratory summary in the placebo-controlled 24-week pool (principal analysis)

	Placebo	Dapagliflozin			
	$n = 1,393$	2.5 mg $n = 814$	5.0 mg $n = 1,145$	10 mg $n = 1,193$	Total[a] $n = 3,291$
≥1 AE	792 (56.9)	493 (60.6)	709 (61.9)	734 (61.5)	2,030 (61.7)
≥1 Treatment-related AE	185 (13.3)	121 (14.9)	197 (17.2)	216 (18.1)	568 (17.3)
≥1 AE leading to discontinuation	35 (2.5)	18 (2.2)	32 (2.8)	38 (3.2)	93 (2.8)
≥1 Serious AE	46 (3.3)	37 (4.5)	40 (3.5)	42 (3.5)	122 (3.7)
≥1 Serious treatment-related AE	5 (0.4)	0	2 (0.2)	2 (0.2)	5 (0.2)
Deaths	1 (0.1)	1 (0.1)	2 (0.2)	3 (0.3)	6 (0.2)
Hepatic disorder (elevated liver enzymes)[b]	$n = 1,382$	$n = 814$	$n = 1,136$	$n = 1,182$	$n = 3,270$
	55 (4.0)	32 (3.9)	40 (3.5)	43 (3.6)	120 (3.7)

Data are *n* (%). *n/N* is the number of treated patients. Includes laboratory values measured on/after the first date/time of 12- or 24-week double-blind treatment and on or prior to the last day of 12- or 24-week double-blind treatment plus 30 days or on or prior to the first day of long-term treatment if earlier

[a] Total includes dapagliflozin 20-mg and 50-mg doses

[b] *n* is the number of patients with at least one nonmissing postbaseline value

AE adverse event

UTIs, back pain, polyuria, dysuria and dyslipidaemia (Table 3). AEs occurring in ≥2 % of patients in any treatment group are listed in the Electronic Supplementary Material 3. Serious AEs were reported for 3.7 % of the dapagliflozin group and 3.3 % of the placebo group. Discontinuations as a result of an AE were few and occurred in similar proportions for placebo (2.5 %) and dapagliflozin (2.8 %) groups.

Analysis of the longer-term placebo-controlled pool showed that the AE profile was consistent with that established in the short-term and the overall proportion of AEs was balanced between treatment groups up to 102 weeks.

Table 3 Adverse drug reactions[a] occurring in dapagliflozin 5- and 10-mg groups in the placebo-controlled 24-week pool (principal analysis)

	Placebo	Dapagliflozin	
	$n = 1{,}393$ (%)	5 mg $n = 1{,}145$ (%)	10 mg $n = 1{,}193$ (%)
Hypoglycaemia[b]	7.0	10.9	10.2
Genital infection[c]	0.9	5.7	4.8
Urinary tract infection[d]	3.7	5.7	4.3
Back pain	3.2	3.1	4.2
Polyuria[e]	1.7	2.9	3.8
Dysuria	0.7	1.6	2.1
Dyslipidaemia	1.5	2.1	2.5

[a] Adverse drug reactions were identified based on the following criteria: (1) reported in ≥2 % of patients in the dapagliflozin 5- or 10-mg groups (regardless of investigator assessment of causality); (2) reported ≥1 % more frequently in the dapagliflozin 5- or 10-mg groups compared with placebo; and (3) reported in three patients more in the dapagliflozin 5- or 10-mg groups compared with placebo

[b] Excludes data after rescue. Adverse reactions of major hypoglycaemia (an episode in which the patient requires assistance or treatment and, if inadequately treated, may be life threatening) were 0.1 % for dapagliflozin 5 mg, 0.1 % for dapagliflozin 10 mg and 0.1 % for placebo. Adverse reactions of hypoglycaemia were primarily from add-on to insulin and add-on to sulfonylurea trials

[c] Genital infection includes the following preferred terms, listed in order of frequency reported: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis *Candida*, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, balanoposthitis, balanoposthitis infective, genitourinary tract infection, posthitis, vaginitis bacterial and vulval abscess

[d] Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, *Escherichia* urinary tract infection, trigonitis, genitourinary tract infection, prostatitis, pyelonephritis, urethritis and urinary tract infection fungal

[e] Polyuria includes the preferred terms, listed in order of frequency reported: pollakiuria, polyuria and urine output increased

In the broader population, observed for up to 2 years, deaths occurred in 0.5 % for both dapagliflozin and control groups.

3.3 Hypoglycaemia

More events of hypoglycaemia occurred in the dapagliflozin group (11.8 %) compared with the placebo group (7.0 %, Table 4), primarily due to the results of the add-on to insulin and sulfonylurea studies (Table 5). No hypoglycaemic events led to discontinuation of study treatment. Major hypoglycaemic episodes were balanced across groups (<1 % of patients).

For monotherapy studies, add-on to pioglitazone and the add-on to metformin studies, hypoglycaemic rates with dapagliflozin treatment were low (<4 %) and, in general, similar to placebo. With dapagliflozin as add-on to sulfonylurea (glimepiride, $n = 597$), hypoglycaemic events were reported for 6.9–7.3 % of individuals receiving dapagliflozin compared with 4.8 % in the placebo group. One major episode of hypoglycaemia was reported in the dapagliflozin 2.5 mg group. In the phase III add-on to insulin study ($n = 807$), overall rates were 42.3–51.5 % in the dapagliflozin groups and 35.0 % in the placebo group. Major episodes of hypoglycaemia were reported in 0.9–1.9 % dapagliflozin and 0.5 % placebo groups. Results from the add-on to insulin study accounted for 83 % of the major and minor hypoglycaemic episodes in the principal pooled analysis.

Overall, results of longer-term analysis in the 102-week placebo-controlled pool were generally similar to that established in the short-term but overall frequencies of events were slightly higher for all treatment groups.

3.4 Urinary Tract Infections

Overall, UTIs occurred slightly more often in patients taking dapagliflozin than in those receiving placebo (4.8 vs 3.7 %, respectively) (Table 4).

Most UTIs were mild to moderate in severity and responded to conventional treatment. In the cases in which urine cultures were performed, the pathogenic organisms were shown to be well established causes of UTIs in the general and diabetic populations, including *Escherichia coli* and *Klebsiella*. UTIs were more common in women. In men the incidence of UTIs was similar amongst patients in the dapagliflozin and placebo groups. The most commonly reported events were UTI and cystitis amongst women and UTI amongst men.

One patient in the placebo group had an event (UTI) that was considered serious. Six patients in the dapagliflozin group discontinued study treatment because of UTI; however, discontinuations were ≤0.5 % in all groups. Recurrence rates were infrequent in both groups though higher

Table 4 Adverse events of special interest in the placebo-controlled 24-week pool (principal analysis)

	Placebo	Dapagliflozin			
	n = 1,393	2.5 mg *n* = 814	5.0 mg *n* = 1,145	10 mg *n* = 1,193	Total[a] *N* = 3,291
Total patients with hypoglycaemia[b]	98 (7.0)	126 (15.5)	125 (10.9)	122 (10.2)	387 (11.8)
Major episode	1 (0.1)	3 (0.4)	1 (0.1)	1 (0.1)	5 (0.2)
Minor episode	75 (5.4)	107 (13.1)	107 (9.3)	99 (8.3)	316 (9.6)
Other episode	19 (1.4)	20 (2.5)	17 (1.5)	22 (1.8)	66 (2.0)
Other episode with plasma glucose level ≥63 mg/dL	*n* = 1,051 15 (1.4)	*n* = 556 14 (2.5)	*n* = 875 14 (1.6)	*n* = 854 17 (2.0)	*n* = 2,424 51 (2.1)
UTI[c]	52 (3.7)	29 (3.6)	65 (5.7)	51 (4.3)	158 (4.8)
n	716	414	564	595	1,643
Male	7 (1.0)	6 (1.4)	9 (1.6)	5 (0.8)	21 (1.3)
n	677	400	581	598	1,648
Female	45 (6.6)	23 (5.8)	56 (9.6)	46 (7.7)	137 (8.3)
Vulvovaginitis, balanitis or related infection[d]	12 (0.9)	33 (4.1)	65 (5.7)	57 (4.8)	167 (5.1)
n	716	414	564	595	1,643
Male	2 (0.3)	10 (2.4)	16 (2.8)	16 (2.7)	45 (2.7)
n	677	400	581	598	1,648
Female	10 (1.5)	23 (5.8)	49 (8.4)	41 (6.9)	122 (7.4)
Total patients with events of hypotension, dehydration or hypovolaemia (volume depletion)[e]	5 (0.4)	10 (1.2)	7 (0.6)	9 (0.8)	27 (0.8)
Hypotension	2 (0.1)	6 (0.7)	5 (0.4)	5 (0.4)	16 (0.5)
Syncope	1 (<0.1)	0	0	2 (0.2)	2 (<0.1)
Dehydration	0	3 (0.4)	0	1 (<0.1)	4 (0.1)
Urine flow decrease	0	0	0	1 (<0.1)	1 (<0.1)
Blood pressure decrease	1 (<0.1)	0	0	0	0
Orthostatic hypotension	0	1 (0.1)	2 (0.2)	0	4 (0.1)
Urine output decreased	1 (<0.1)	1 (0.1)	0	0	1 (<0.1)
Total patients with elevated haematocrit[f] and/or embolic and thrombotic events	17 (1.2)	23 (2.8)	24 (2.1)	36 (3.0)	86 (2.6)
Elevated haematocrit only	7 (0.5)	18 (2.2)	15 (1.3)	29 (2.4)	65 (2.0)
Embolic and thrombotic events only	10 (0.7)	5 (0.6)	8 (0.7)	7 (0.6)	20 (0.6)
Both elevated haematocrit and embolic and thrombotic events	0	0	1 (0.1)	0	1 (<0.1)

Data are *n* (%). *n*/*N* is the number of treated patients

[a] Total includes dapagliflozin 20 mg and 50 mg doses

[b] Excludes data after rescue. Includes hypoglycaemia events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of on or prior to the last day of 12- or 24-week double-blind treatment plus 4 days or up to and including the start date of extension periods, if earlier. Major episode defined as a symptomatic episode requiring external assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value <3 mmol/L (<54 mg/dL) and prompt recovery after glucose or glucagon administration. Minor episode defined as either a symptomatic episode with a capillary or plasma glucose measurement <3.5 mmol/L (63 mg/dL), regardless of need for assistance, or an asymptomatic capillary or plasma glucose measurement <3.5 mmol/L (63 mg/dL) that does not qualify as major episode. Other episode of hypoglycaemia defined as suggestive episode reported but not meeting the criteria for major or minor episodes. The category 'other episode with plasma ≥63 mg/dL' defined as symptoms suggestive of hypoglycaemia with plasma glucose ≥63 mg/dL. This definition was used for the majority of studies. For the Add-on to sulfonylurea, the Add-on to metformin vs sulfonylurea, the Add-on to metformin (body composition) and the Add-on to insulin studies, plasma glucose ≥63 mg/dL criteria was not considered hypoglycaemia and symptoms were reported as an adverse event instead

[c] Includes non-serious/serious adverse events with onset during the double-blind treatment through follow-up visit after treatment end or start of a long-term extension period. Based on predefined lists of preferred MedDRA Version 13.0 terms that are indicative of urinary tract infections

[d] Includes non-serious/serious adverse events with onset during the double-blind treatment through follow-up visit after treatment end or start of a long-term extension period, based on predefined lists of preferred MedDRA Version 13.0 terms that are indicative of vulvovaginitis, balanitis or related infections

[e] Includes non-serious/serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of 12- or 24-week double-blind treatment plus 4 days/30 days or up to and including the start date of the study extension period or up to the follow-up visit if earlier. Based on a predefined list of preferred MedDRA Version 13.0 terms that indicate hypotension/dehydration/hypovolaemia

[f] Based on measured laboratory values. Criteria based on either haematocrit >55.0 % or haemoglobin >18 g/dL

Table 5 Hypoglycaemia stratified by monotherapy and add-on therapies

	Placebo	Dapagliflozin		
		2.5 mg	5 mg	10 mg
Placebo-controlled pool	$n = 1,393$	$n = 814$	$n = 1,145$	$n = 1,193$
%	7.0	15.5	10.9	10.2
Monotherapy pool	$n = 251$	$n = 321$	$n = 316$	$n = 245$
%	2.0	2.5	2.2	2.9
Add-on combination + metformin pool	$n = 228$	–	–	$n = 226$
%	3.1			3.1
+Pioglitazone	$n = 139$	–	$n = 141$	$n = 140$
%	0.7		2.1	0
+Sulfonylurea	$n = 146$	$n = 154$	$n = 145$	$n = 151$
%	4.8	7.1	6.9	7.3
+Insulin	$n = 197$	$n = 202$	$n = 212$	$n = 196$
%	35.0	51.5	45.3	42.3

Data excluding rescue

for the dapagliflozin group (16.4 % of those with UTI) than the placebo group (7.7 %). Patients with a history of recurrent UTI were also more likely to have an event than those who did not, irrespective of treatment group.

Results were similar in the longer-term, 102-week placebo-controlled pool, but with a slightly higher total number of events. Additionally, long-term analyses showed that first events were more likely to occur in the first 24 weeks than after 24 weeks in all treatment groups.

In the broader 14-studies pool with observations up to 102 weeks, events of kidney infection were rare: three patients each in the dapagliflozin (0.1 %) and control (0.2 %) groups experienced pyelonephritis. Of these, two events were considered serious AEs and both occurred in the control group.

3.5 Genital Infections

For all doses of dapagliflozin, the observed rates of vulvovaginitis, balanitis and other related infections were higher than placebo (5.1 vs 0.9 %, Table 4). Most events ($\geq$97 %) were mild to moderate in intensity. Of the 209 events reported in 167 dapagliflozin-treated patients, three were severe (one in the 2.5 mg group and two in the 5 mg group) and none were serious. Two (0.2 %) patients were discontinued (one each with vulvovaginal mycotic infection and balanitis in the dapagliflozin 10 mg group). The most common events were vulvovaginal mycotic infection (including infections with *Candida*) and vaginal infection in females, and balanitis fungal genital infection and balanitis candida in males. Genital infections were more common in females. Most events resolved spontaneously or responded to an initial course of antimicrobial treatment. For patients receiving dapagliflozin, 75.1 % of events were treated with antimicrobial therapy and, of 209 total events, 4.3 % required a second course of treatment. Recurrence rates were low in both groups and higher for the dapagliflozin group (17.4 % of those with genital infections) compared with the placebo group (8.3 %).

Results were similar in the longer term 102-week placebo-controlled pool, but with a slightly higher total number of events. In all treatment groups, first events were more likely to occur in the first 24 weeks than after 24 weeks.

3.6 Renal Function

At baseline, most patients in the placebo-controlled pool had normal renal function (eGFR >90 mL/min/1.73 m^2; 36.9–39.7 %) or mild renal impairment (eGFR 60–90 mL/min/1.73 m^2; 52.8–54.4 %) and 7.5–9.3 % had moderate impairment (eGFR 30–59 mL/min/1.73 m^2). Patients with eGFR <30 mL/min/1.73 m^2 were excluded from studies because of an expected lack of efficacy. Similar proportions of patients in the dapagliflozin and placebo groups had renal events in the placebo-controlled pool (1.2 % in the dapagliflozin group and 0.9 % in the placebo group). These events were mostly laboratory-based events that were pre-specified in the protocol, transient, non-severe and reversible. No event was considered to be serious. For all eGFR categories, the proportion of patients who shifted from a baseline urinary albumin:creatinine (UACR) category to a worse category was the same or lower for dapagliflozin groups compared with placebo at week 24.

In the longer-term, 102-week pool, 2.0 % in the dapagliflozin group and 1.6 % in the placebo group had renal events. Serious renal events were reported in one patient each in the dapagliflozin 2.5 and 5 mg groups and in the placebo group. Dapagliflozin treatment was associated with a transient decrease in eGFR at week 1 that was followed by a return to baseline values (82.53 mL/min/1.73 m^2) or above. Thereafter eGFR was stable over time (observed up

to 2 years) in the placebo-controlled pool. At week 102, increases from baseline in mean eGFR were observed in both groups: 2.02 mL/min/1.73 m^2 in the dapagliflozin group and 0.66 mL/min/1.73 m^2 in the placebo group.

In the broader, 14-studies pool, a similar number of serious renal events were reported in the dapagliflozin ($n = 4$) and control groups ($n = 4$).

Overall, the data showed no imbalance in serious events between groups and no evidence of new or worsening renal impairment, progression of diabetic nephropathy, acute nephrotoxicity or other events suggesting toxic or immunologically mediated nephropathy in dapagliflozin-treated patients up to 2 years.

3.7 Hypotension/Dehydration/Hypovolaemia

Hypotension, dehydration and hypovolaemia events were grouped as volume-related events. Overall, such events were infrequent but were more often reported in the dapagliflozin group versus the placebo group (0.8 vs 0.4 % in the 12–24 week period), with no dose dependence (Table 4) and none were considered serious. Hypotension was the most commonly reported event related to volume depletion. Events reported as orthostatic hypotension were infrequent. Measured orthostatic hypotension (defined as a decrease from supine to standing systolic BP >20 mmHg or diastolic BP >10 mmHg) was 10.7 % for the total dapagliflozin group (baseline 4.1 %) and 9.2 % for the placebo group (baseline 3.2 %). A higher risk of hypotension, hypovolaemia or dehydration events for dapagliflozin versus placebo treatment was observed in patients receiving loop diuretics (6.1 vs 1.8 %).

Overall, the proportion of patients with volume-related events after up to 102 weeks of treatment was consistent with that observed in the short term.

In the broader, 14-studies pool, there were four serious volume-related events each in the dapagliflozin and control groups.

3.8 Haematology and Thromboembolic Events

Most patients experienced small increases in haematocrit and haemoglobin in the first 12–16 weeks of dapagliflozin treatment, contributing to an overall small mean increase for patients treated with dapagliflozin. At week 24, the mean change from baseline in haematocrit levels was 1.9 % (baseline 42.4 %) in the dapagliflozin group and −0.40 % (baseline 42.5 %) in the placebo group (Table 4). No further increases were observed, and levels were stable after 12–16 weeks.

Predefined laboratory-reported marked abnormalities related to increased haematocrit or haemoglobin (haematocrit >55 % or haemoglobin >18 g/dL) were reported in more dapagliflozin-treated patients (2.6 %) than placebo (1.2 %). Increases in haematocrit reported during treatment were not related to thromboembolic events. One patient in the dapagliflozin group who had an elevated haematocrit at baseline and a history of multiple CV risk factors, and who reported haematocrit marked abnormalities during the study, developed worsened peripheral artery disease requiring thrombarterectomy.

Results of longer-term analysis in the 102-week placebo-controlled pool were generally consistent with that established in the short term.

3.9 Urinary Stones

Urinary stones were reported infrequently across the broader 14-studies pool. Numbers of urinary stones reported were lower in patients treated with dapagliflozin (0.6 %) versus comparator (1.2 %).

3.10 Fractures

In the 14-studies pool, small but similar proportions of patients in the dapagliflozin and all control groups reported fractures during the short-term plus long-term treatment study periods (1.2 % in each group). There was no pattern in the anatomical facture site. The most common sites of fracture were foot (0.2 % dapagliflozin groups vs 0.1 % all control groups) and ankle (0.2 % in each group). Analysis of pooled dapagliflozin monotherapy and add-on to metformin trials were consistent with findings from the pooled analysis of placebo-controlled studies. In these cases, the proportion of fractures in any treatment group, was <2 %. In patients with moderate renal impairment, more dapagliflozin-treated patients (5 mg, 3.6 %; 10 mg, 8.2 %) reported fractures compared with none in the placebo arm. A similar pattern was observed in the add-on to insulin study (0.5, 3.3, and 2.6 % in the dapagliflozin 2.5, 5, and 10 mg groups, respectively, versus 2.0 % in the placebo group).

3.11 Hepatic Events

There was no imbalance in the proportion of patients with elevated parameters associated with abnormal liver functions in the placebo-controlled pool (dapagliflozin, 3.7 % and placebo, 4.0 %) (Table 2). At week 24, mean total bilirubin levels increased from baseline in the dapagliflozin group (0.34 μmol/L [0.02 mg/dL]; baseline 9.07 μmol/L [0.53 mg/dL]), with no dose dependence, and decreased in the placebo group (−0.17 μmol/L [−0.01 mg/dL]; baseline 8.89 μmol/L [0.52 mg/dL]). Mean alanine aminotransferase (ALT) levels decreased from baseline in both dapagliflozin (0.07 μkat/L [−3.9 U/L]; baseline 0.50 μkat/L [29.8 U/L]) and placebo groups (−0.03 μkat/L [−1.7 U/

L]; baseline 0.51 μkat/L [30.3 U/L]). A similar decrease from baseline was observed for mean aspartate aminotransferase (AST) levels in both dapagliflozin (−0.03 μkat/L [−2.0 U/L]; baseline 0.40 μkat/L [24.2 U/L]) and placebo groups (−0.02 [μkat/L] −1.1 U/L; baseline 0.40 μkat/L [24.0 U/L]).

In terms of rare events, increases of ALT and AST were balanced in all treatment groups in the broader 14-studies pool. Across this pool ($n = 6,228$), eight patients met the criteria of abnormal liver enzyme increments, ALT or AST >3 times the upper limit of normal and concomitant or subsequent total bilirubin >2 times the upper limit of normal (within 30 days after discontinuation of study medication): five (0.1 %) treated with dapagliflozin and three (0.2 %) with a comparator (two with placebo; one with glipizide). Seven patients had underlying causes of these elevations unrelated to the study treatment and one patient had an acute hepatitis with an alternative diagnosis of drug-induced liver injury or autoimmune hepatitis, which was originally independently adjudicated as 'possibly' related (25–49 % likelihood) to dapagliflozin use. Following study drug discontinuation, enzyme levels were decreased but still slightly elevated. The patient was started on steroids and subsequently on azathioprine, which resulted in normalization of liver test results. During continued immunosuppression and absence of dapagliflozin, two episodes with enzyme elevation (ALT/AST) were observed in the 3 years after study drug was discontinued and the patient required long-term immunosuppression for the diagnosis of autoimmune hepatitis.

3.12 Malignancies

The overall incidence of malignancies and unspecified tumours was balanced across groups, with 81/5,501 (1.5 %) patients in the dapagliflozin group and 43/3,184 (1.4 %) in the placebo group. The incidence rate (95 % CI) for malignancy and unspecified tumours per 100 patient-years was 1.39 (1.10, 1.72) in the dapagliflozin group and 1.34 (0.97, 1.81) in the control group. Figure 2 illustrates that all organ categories had CIs overlapping unity (indicating that there was no statistically significant difference between treatment groups). There were six organ systems with incidence rate ratio estimates above unity, including breast, prostate and bladder; seven organ systems with an incidence rate ratio below, including renal tract, female reproductive and metastases/site unspecified; and one organ system with insufficient observations for statistical analysis.

	Events	
	Dapagliflozin $n = 5501$	Control $n = 3184$
Patients with tumour events [a]	81	43
Tumour origin		
Bladder	9	1
Prostate (male only)	10	3
Breast (female only)	10	3
Hepatobiliary	3	1
Pancreatic	5	2
Thyroid and endocrine	7	4
Skin	15	10
Respiratory and mediastinal	8	6
Gastrointestinal	6	4
Blood and lymphatic	3	3
Metastases and site unspecified	2	2
Female reproductive	1	2
Renal tract	1	2
Musculoskeletal and soft tissue	1	0

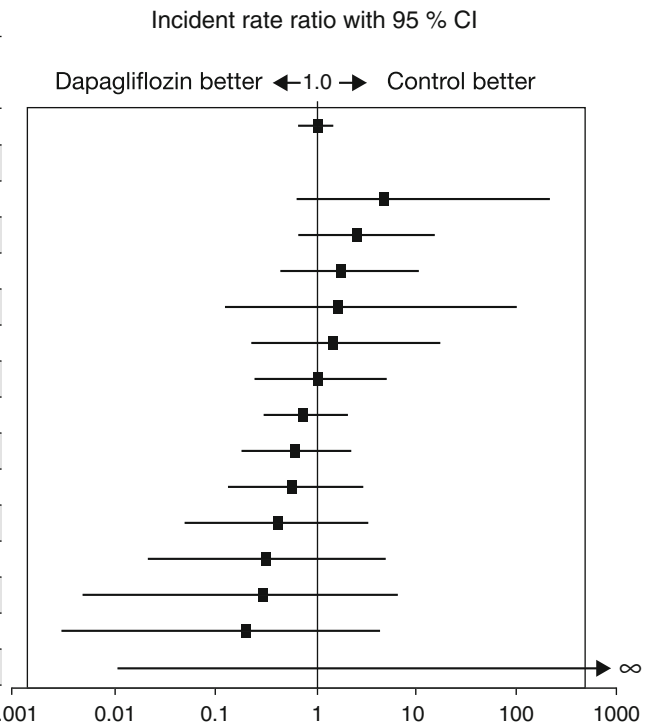

Fig. 2 Incidence rate ratio and 95 % confidence interval for diagnosed malignancies for dapagliflozin versus control by organ system for all studies. [a] There were one and zero subjects in the dapagliflozin and control groups, respectively, leading to an incidence rate ratio point estimate of infinity

The incidence rate of breast cancer in females per 100 patient-years was 0.37 (0.18, 0.68), and 0.22 (0.05, 0.64) for the dapagliflozin group and control group, respectively, with inconclusive statistical analyses (incidence rate ratio 1.903 [95 % CI 0.461, 11.230]). All breast tumours were diagnosed within 1 year of study start.

The incidence rate of prostate cancer in males per 100 patient-years, was 0.32 (0.15, 0.58), and 0.16 (0.03, 0.47) for the dapagliflozin and control groups, respectively. Three of ten cases in the dapagliflozin group were clearly pre-existing: two cases were diagnosed within the first week of treatment and a third case was a recurrence of a pre-existing cancer and was diagnosed 49 days after the start of dapagliflozin treatment. An additional case in the dapagliflozin group was found to be non-malignant. A single event in the comparator group was reported spontaneously more than a year after discontinuation of treatment.

The incidence rate of bladder cancer per 100 patient-years, was 0.15 (0.07, 0.29), and 0.03 (0.00, 0.17) for the dapagliflozin and control groups, respectively. Bladder tumours were all diagnosed within 2 years of study start and in most cases there was haematuria before treatment commenced (6/9 dapagliflozin; 1/1 comparator). Typical clinical characteristics, including histology, were observed for breast, bladder and prostate cancer and no histological evidence was found for fast-growing or unusual tumours.

3.13 Serum Electrolytes, Uric Acid and Related Laboratory Parameters

Changes in mean serum electrolytes and marked abnormalities (Electronic Supplementary Material 4) were infrequent. In the placebo-controlled pool, there were no changes from baseline levels of mean serum sodium, potassium, bicarbonate, calcium or chloride at week 24 and up to 102 weeks. Small increases in mean serum inorganic phosphorus levels from baseline (1.2 mmol/L [3.6 mg/dL]), within the range of normal, were reported at week 24 in the dapagliflozin (0.05 mmol/L [0.15 mg/dL]) and placebo (0.01 mmol/L [0.03 mg/dL]) groups. At 24 weeks, mean parathyroid hormone (PTH) levels increased slightly from baseline in the dapagliflozin groups (2.0 ng/L [equivalent to pg/mL]; baseline 37.6 ng/L), within normal limits and with no dose-dependent effect, compared with decreased levels in the placebo group (−0.6 ng/L; baseline 36.6 ng/L). Similar changes in inorganic phosphorus and PTH were observed at 102 weeks.

Small mean increases in serum magnesium levels from baseline (0.86 mmol/L [1.71 mEq/L]) were reported at week 24 in the dapagliflozin group (0.03 mmol/L [0.06 mEq/L]), compared with a decrease in the placebo group (−0.02 mmol/L [−0.04 mEq/L]). At week 102, the mean change from baseline (0.85 mmol/L [1.70 mEq/L]) in the dapagliflozin groups was −0.04 mmol/L (−0.08 mEq/L), compared with −0.08 mmol/L [−0.16 mEq/L] in the placebo group.

Uric acid levels decreased in all dapagliflozin groups in the studies in which it was analysed. Placebo-corrected mean reductions in plasma uric acid levels ranged from −29.7 to −47.6 μmol/L (−0.5 to −0.8 mg/dL) in the three placebo-controlled studies (monotherapy, monotherapy with low-dose dapagliflozin and add-on to metformin). No excess in gout episodes was associated with dapagliflozin treatment versus placebo.

3.14 Fasting Low- and High-Density Cholesterol, Triglycerides and Free Fatty Acids

During the short-term period, the mean percent change from baseline to week 24 in high-density lipoprotein cholesterol was 3.8–6.5 % in the dapagliflozin groups and 3.8 % in the placebo group, in low-density lipoprotein cholesterol, 0.6–2.7 % in the dapagliflozin groups and −1.9 % in the placebo group; in total cholesterol, 1.0–1.4 % in the dapagliflozin groups and −0.4 % in the placebo group; in triglycerides, −3.2 to −5.4 % in the dapagliflozin groups and −0.7 % in the placebo group; and in free fatty acids, −0.5 to 1.2 % in the dapagliflozin groups and –5.7 % in the placebo group.

3.15 Supplementary Analyses: Older Patients and Those With Renal Impairment

The incidence and nature of AEs in patients aged ≥65 years was similar to that observed in the overall population and in patients <65 years. Consistent with the overall population, AEs were reported by a slightly higher proportion of patients aged ≥65 years ($n = 907$) for dapagliflozin (62.1 %) versus placebo (55.8 %) groups. Similar proportions of patients aged ≥75 years ($n = 89$) reported AEs in the dapagliflozin (56.7 %) and placebo (59.1 %) groups. A higher proportion of patients aged ≥75 years ($n = 70$) treated with dapagliflozin (74.5 %) than with placebo (60.0 %) reported AEs in the 102-week pool. In patients aged ≥65 years, AEs of renal impairment/failure (dapagliflozin, 2.5 %, placebo, 1.1 %) were higher for dapagliflozin than placebo groups in the 24-week pool. Additionally, AEs of hypotension/dehydration/hypovolaemia (dapagliflozin, 1.6 %, placebo, 0.4 %) were more frequent for dapagliflozin than placebo groups.

In an analysis of moderate renal impairment (baseline eGFR ≥30 and <60 mL/min/1.73 m^2) in the placebo-controlled pool, the incidence of AEs of renal impairment or failure was 8.3 % ($n = 23/277$) and 5.6 % ($n = 6/107$) in the dapagliflozin and placebo groups, respectively. The

proportion of patients who shifted from normoalbuminuria to a higher category of proteinuria was lower in the dapagliflozin group (10.1 %; $n = 18/179$) than the placebo group (13.2 %; $n = 10/76$). Shifts in microalbuminuria to macroalbuminuria were similar (dapagliflozin 0 %, $n = 0/77$ vs placebo 3.7 %, $n = 1/27$). Dapagliflozin and placebo groups had low rates of hyperkalaemia (0.4 and 0 %, respectively) and fracture (0 and 1.9 %, respectively) in this subgroup.

4 Discussion

These pooled analyses comprehensively describe the safety profile of dapagliflozin in 12 placebo-controlled, pooled studies, and further investigate rare events compiling data from across the available data from the phase IIb/III clinical programme in studies lasting up to 102 weeks.

The various patient populations evaluated in these analyses are representative of the general population of patients with T2DM, in terms of age, concomitant antihyperglycaemic and antihypertensive medication and disease duration. Likewise, studies were included that addressed patients at a greater risk of CV disease (patients with co-morbid hypertension and previous CV events) and patients with mild and moderately impaired renal function, both common co-morbid conditions for patients with diabetes.

Hypoglycaemia is a concern for all antidiabetic agents. Dapagliflozin showed little propensity to cause hypoglycaemia in studies in which it was given as monotherapy or in combination with other treatments that have a low hypoglycaemic potential, including metformin and thiazolidinediones. This is also in line with results from a 52-week head-to-head comparison of dapagliflozin versus glipizide as add-on to metformin ($N = 597$), where rates of hypoglycaemia were significantly lower with dapagliflozin (3 %) than with glipizide (40 %, $p < 0.0001$) [5]. This is likely due to dapagliflozin's mechanism of action, which is independent of insulin and does not cause hyperinsulinaemia. Additionally, while dapagliflozin treatment reduces kidney glucose reabsorption, it does not compromise the counter-regulatory pathways, thus adaptation to low blood glucose is not impaired [24].

Adding dapagliflozin to insulin or sulfonylurea moderately increases the risk for hypoglycaemia because these agents intrinsically have a high hypoglycaemia risk. Although major hypoglycaemic events occurred infrequently, this increased risk should be considered and may necessitate a dose adjustment for insulin or sulfonylureas when given in combination with dapagliflozin.

Patients with diabetes are at risk for nephropathy and because dapagliflozin's mechanism of action targets renal action, we specifically evaluated potential effects on kidney function by carefully assessing a broad list of kidney-related MedDRA® terms and laboratory parameters associated with renal function. There was no evidence of substantial impact on renal function as measured by eGFR, UACR, or laboratory values. A transient decrease in eGFR, observed early in the treatment course, was not associated with AEs and likely reflects haemodynamic changes related to diuresis and a reduction in BP [25]. Alternatively, withdrawal of the tubuloglomerular feedback may explain or contribute to the early drop in eGFR later stabilizing following a transient natriuresis [26]. Overall, the pooled analyses indicate no renal toxic effects associated with dapagliflozin.

Due to the chronic glucosuria associated with dapagliflozin, there was an initial concern that the risk of infections might dramatically increase. However, UTI was only slightly elevated above placebo in the dapagliflozin program. Moreover, the incidence of serious infections, such as pyelonephritis, was rare and balanced between study groups. An increase in fungal genital infections of vulvovaginitis/balanitis was observed with dapagliflozin treatment. Importantly, most events of UTI or genital infection were mild to moderate in severity, had similar clinical characteristics to those routinely encountered in clinical practice, and responded well to standard antibiotic or antimycotic treatment when appropriate.

Aside from infections, the safety profile of dapagliflozin primarily reflects its mild osmotic diuretic effect. Predictable, diuresis-related effects observed with dapagliflozin treatment included small changes in electrolytes; events of dehydration and intravascular volume reduction, mostly reported as hypotension; small mean increases in haematocrit, dysuria, and pollakiuria; and a trend toward lower BP that could be potentially beneficial. Electrolyte changes were limited to small increases in serum phosphorus and magnesium, which did not appear to be clinically meaningful. There was a decrease in uric acid levels associated with uricosuria with dapagliflozin; however, urinary stones were reported less frequently in patients receiving dapagliflozin versus comparator. Clinicians should be aware of diuresis-related effects and should counsel patients at risk of volume depletion, and, in the case of actual volume depletion (for instance, with intercurrent gastroenteritis), interrupt treatment. An additional consideration is that dapagliflozin in combination with other diuretic medications may have additive effects.

In patients receiving dapagliflozin, small mean increases in serum phosphorus and PTH levels, which remained within the normal range, were also likely diuresis related. Changes in these markers, often related to bone metabolism, were not associated with changes in bone mineral density as measured by dual-emission X-ray absorptiometry (add-on to metformin [body composition] study) [27] or

with clinical fractures. These findings are also consistent with data from preclinical toxicology studies conducted in dogs (data on file).

An imbalance in fracture incidence with dapagliflozin compared with placebo has been reported in patients with T2DM and moderate renal impairment [28]; however, in the pooled analysis, the proportion of patients with AEs of fracture was small and balanced between the dapagliflozin and comparator groups.

Because T2DM requires long-term treatment and a significant proportion of these patients are older, analyses were conducted to assess long-term safety and safety in a population aged ≥65 years. The interpretation of longer-term safety is restricted by the number of long-term extensions available for analysis. Nonetheless, AEs observed up to 2 years were similar to those observed in the shorter analyses and support a predictable safety profile. Moreover, the rate of discontinuation for AEs was small and similar for all groups. Safety analyses in patients aged ≥65 years were similar to the overall population supporting that dapagliflozin is well tolerated in an older population. Importantly, the incidence of renal impairment or failure and volume-related events in these patients was low (≤2.5 %) and events were transient, reversible, non-severe and consistent with a mild diuretic effect. A subgroup of patients aged ≥75 years was also analysed; however, this population included only 17–27 patients per treatment group in the current analysis and therefore may not be truly representative of this population.

Rare, off-target effects are difficult to assess in controlled clinical trials of limited duration; however, the large data set and number of 2-year studies partially mitigate this inherent limitation. In these studies, no clinically relevant off-target effects were identified for dapagliflozin. There was no imbalance in elevated parameters associated with abnormal liver function observed in patients treated with dapagliflozin or comparators. Although a single patient was diagnosed with acute hepatitis that was originally adjudicated as 'possibly' related to dapagliflozin, further follow-up after study drug discontinuation suggests dapagliflozin involvement was unlikely and instead the hepatitis was probably autoimmune. Additionally, in preclinical studies, no safety signals were observed with regards to liver toxicity [24]. Overall, these results indicate that dapagliflozin is not associated with hepatotoxic effects.

In the entire programme, there was an overall balance in total malignancies. This is consistent with preclinical evidence that showed no genotoxicity or carcinogenicity in animal models. Although there was a numerical imbalance in the incidence of some tumour types, there was no statistically significant difference between treatment groups.

The proportion of dapagliflozin-treated women diagnosed with breast cancer is similar to the overall incidence in the female T2DM population [29]. Moreover, the incidence ratio rate of breast cancer for dapagliflozin versus control has decreased with the inclusion of additional patient experience reported here compared with earlier analysis. This reduction over time would be anticipated in the absence of a causal association between dapagliflozin and breast cancer, due to the instability of estimates based on small numbers. Overall, this suggests that the observed imbalance may be attributed to chance or a higher detection rate in the dapagliflozin arm, possibly related to dapagliflozin-induced weight loss, which could have contributed to easier tumour detection in some cases.

Some events of prostate cancer were diagnosed very early in the programme (within weeks), suggesting that these tumours were pre-existing and possibly had a higher rate of detection. Taking into account the 1.7-times greater exposure in the dapagliflozin group for men, the clinical data do not indicate any imbalance across treatment groups.

Similarly, for the cases of bladder cancer, the observational time was too short for dapagliflozin to have had an effect on bladder tumour development or growth rates and the timing of unexplained haematuria suggests the presence of pre-existing tumours before randomization that were diagnosed more often in the dapagliflozin treatment arms possibly due to a higher rate of detection.

The development programme of dapagliflozin is large, which has likely contributed to the fact that rare events of cancer were detected. However, the overall number of events remains too small to draw firm conclusions on the imbalances between the groups. Whilst there is no plausible reason to believe that there is an association between dapagliflozin and the development of cancer, on-going studies will further evaluate long-term safety.

5 Conclusion

The results of this pooled safety analysis suggest a favourable tolerability profile for dapagliflozin. Frequently observed events were consistent with its mechanism of action, were mild in intensity and manageable. Moreover, this profile was consistently observed in individual studies, across a range of patients and in combination with other antidiabetic agents. The low rates of hypoglycaemia, long-term safety data and discontinuations observed in this clinical programme, suggest that dapagliflozin may be used for the long-term treatment of T2DM in a broad spectrum of patients. The safety profile of dapagliflozin will continue to be evaluated as further experience and data are gathered from the clinical trial programme.

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Conflict of interest Agata Ptaszynska, Anne Marie Apanovitch. and James F. List. are employees and shareholders of Bristol-Myers Squibb. Kristina M. Johnsson is an employee of AstraZeneca. Shamik J. Parikh and Tjerk W.A. de Bruin are employees and shareholders of AstraZeneca.

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