Proposed Title: Correction of anemia by dapagliflozin in patients with type 2 diabetes

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Abstract: (Word count = 199/200)

Aims: Anemia is common in type 2 diabetes (T2D), particularly in patients with kidney impairment, and often goes unrecognized. Dapagliflozin treatment increases hemoglobin and serum erythropoietin levels. We investigated the effect of dapagliflozin 10-mg/day on hemoglobin in T2D patients with and without anemia.

Methods: Data from 5325 patients from 14 placebo-controlled, dapagliflozin-treatment studies of at least 24-weeks duration were pooled. Dapagliflozin's effects (vs. placebo) on hemoglobin, serum albumin, estimated glomerular filtration rate (eGFR), systolic blood pressure, body weight, and safety in patients with and without anemia were evaluated.

Results: At baseline, 13% of all T2D patients and 28% of those with chronic kidney disease (eGFR <60 mL/min/1.73 m^2) had anemia. Hemoglobin increased continuously to at least week 8 and was sustained throughout 24-weeks follow-up in dapagliflozin-treated patients. Serum albumin increased in dapagliflozin-treated patients at week 4 and remained stable thereafter. Dapagliflozin was well tolerated and corrected anemia in 52% of patients with anemia at baseline (placebo: 26%). Incidences of new-onset anemia were lower in dapagliflozin-treated (2.3%) versus placebo-treated (6.5%) patients.

Conclusions: Treatment with dapagliflozin can correct and prevent anemia in T2D patients. A gradual increase in hemoglobin beyond week 4 indicates an erythropoiesis-stimulating effect of sodium-glucose cotransporter 2 inhibition.

Key words: Anemia, Chronic kidney disease, Dapagliflozin, Hemoglobin, Type 2 diabetes

Running title: Correction of diabetic anemia with dapagliflozin

1. Introduction

Anemia is a common comorbidity in patients with diabetes and chronic kidney disease (CKD).[1, 2] Furthermore, in patients with diabetes, anemia occurs earlier during the course of kidney disease progression and is more severe than in patients without diabetes.[1-3] Additionally, anemia has been identified as an independent predictor of CKD progression, regardless of the presence of diabetes.[4] In patients with diabetes, anemia is also a risk factor for adverse cardiovascular disease (CVD) outcomes, such as myocardial infarction/fatal coronary heart disease, stroke, and all-cause mortality, especially if individuals also have CKD.[5] In patients with heart failure, anemia is associated with an increased risk of hospitalization and all-cause mortality.[6-9] However, although anemia is common in patients with diabetes and CKD, it often remains unrecognized.[2, 10]

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a class of oral glucose-lowering agents approved for the treatment of type 2 diabetes (T2D).[11] Treatment of patients with T2D with dapagliflozin, a highly selective SGLT2i, is associated with stabilization of estimated glomerular filtration rate (eGFR) and reductions in glycated hemoglobin (HbA_{1c}), systolic blood pressure (SBP), body weight, and albuminuria.[12-15] Studies have shown a small and consistent increase in hematocrit with dapagliflozin treatment in patients with T2D and normal kidney function.[16,17] This hematocrit elevation, associated with dapagliflozin treatment, has been attributed to hemoconcentration due to a mild diuretic effect resulting in a decrease in plasma volume.[14] In addition to its effect on hematocrit, SGLT2i result in a transient increase in reticulocyte count and serum erythropoietin concentration.[14,18] Further investigation of the effect of dapagliflozin on hemoglobin (Hb) concentration is therefore warranted. The objective of the current *post hoc* analysis was to evaluate the effect of dapagliflozin 10-mg/day treatment over 24 weeks on Hb

concentrations, serum albumin, eGFR, SBP, and body weight in patients with T2D with and without anemia at baseline.

2. Materials and methods

2.1 *Study design*

This *post hoc* analysis pooled data from 14 placebo-controlled, phase 2 and 3, double-blind clinical trials in patients with T2D (N = 5325; Supplementary Table 1). To examine the effect of dapagliflozin in patients with established anemia and to help differentiate between hemoconcentration and hematopoietic effects, we divided the population according to baseline Hb into anemia (Hb <13 g/dL in men and <12 g/dL in women) and no-anemia groups based on criteria defined by the World Health Organization. Fourteen trials included dapagliflozin monotherapy treatment arms and were included in the analysis. All trials were part of the dapagliflozin clinical development program and were not designed to examine the effect of dapagliflozin on anemia. The trial protocols did not include specific recommendations or restrictions regarding diet or supplemental iron. Information on patient ethnicity was not recorded across all trial sites and is, therefore, not reported in the current analysis, although data on race were available and are reported. All clinical study protocols were approved by the relevant institutional review board/ethics committee, and written informed consent was provided by the enrolled patients. The trials were conducted in accordance with the principles of the Declaration of Helsinki.

2.2 *Outcomes*

We evaluated the change in Hb over 24 weeks in patients receiving dapagliflozin or placebo in the anemia and no-anemia groups. Blood samples were collected and analyzed at a

central laboratory as part of the standard clinical trial safety assessment during the individual clinical trials; Hb was measured at baseline and at weeks 4, 8, 12, 16, 20, and 24. We evaluated the change in Hb in patients with or without baseline anemia and determined the proportion of patients with baseline anemia who were no longer anemic at week 24.

Changes from baseline to week 24 in eGFR (calculated using the Modification of Diet in Renal Disease Study equation), serum albumin, SBP, and body weight were also evaluated. CKD was defined as eGFR <60 mL/min/1.73 m^2. Safety outcomes included the occurrence of adverse events (AEs) and serious adverse events (SAEs), including those of special interest (renal impairment, urinary tract infection, and volume depletion). Occurrence of polycythemia (Hb >16.5 g/dL in men and >16.0 g/dL in women) was also evaluated.

2.3 *Statistical analysis*

Descriptive statistics were used for presenting baseline characteristics and safety data. For efficacy parameters, the mean changes from baseline values and 95% confidence intervals (CIs) using a longitudinal repeated-measures mixed model with fixed terms for study, treatment, week, group, week-by-treatment interaction, treatment-by-group interaction, week-by-group interaction, and treatment-by-week-by-group interaction, along with the fixed covariates of baseline, baseline-by-study interaction, and baseline-by-week interaction, were derived. The Kenward-Roger method was used to approximate the degrees of freedom in the mixed model. In the event that the model(s) did not converge, either the Satterthwaite approximation was employed or the models were re-run using the Kenward-Roger method with the baseline-by-study and baseline-by-week terms removed.

3. Results

3.1 Baseline characteristics

A total of 5325 patients were included in the study: 700 (13%) in the anemia group and 4625 (87%) in the no-anemia group (Table 1). In total, 1168 patients (21.9%) had CKD and anemia was more common in this group (28% vs. 9% with and without CKD, respectively; Supplementary Fig. 1).

Overall, 46.3% of patients in the anemia group had CKD (mean eGFR: 66.3 mL/min/1.73 m^2) compared with 18.3% of patients in the no-anemia group (mean eGFR: 78.6 mL/min/1.73 m^2). Additionally, 49.3% of patients with anemia had increased albuminuria (urine albumin-to-creatinine ratio [UACR] >30 mg/g) at baseline (median UACR = 30 mg/g) compared with 30.1% of patients with no anemia (median UACR = 11 mg/g).

Patients with anemia were slightly older (mean age: 63 vs. 59 years), had a longer history of T2D (mean duration: 14 vs. 9 years), and were more often black/African American (10% vs. 3%).

3.2 Effect of dapagliflozin on Hb concentrations

Treatment with dapagliflozin resulted in a gradual increase in Hb concentration (Fig. 1A). In the anemia group, the adjusted mean changes in Hb from baseline at week 24 were 0.81 g/dL (95% CI: 0.68, 0.93) with dapagliflozin and 0.28 g/dL (95% CI: 0.15, 0.41) with placebo. The placebo-adjusted mean change in Hb upon treatment with dapagliflozin at week 24 was 0.53 g/dL (95% CI: 0.38, 0.68). In the no-anemia group, the adjusted mean changes in Hb from baseline at week 24 were 0.56 g/dL (95% CI: 0.53, 0.61) with dapagliflozin and −0.20 g/dL (95% CI: −0.23, −0.16) with placebo. The placebo-adjusted mean change in Hb upon treatment with dapagliflozin at week 24 was 0.76 g/dL (95% CI: 0.72, 0.81). The placebo-adjusted increase in Hb upon treatment with dapagliflozin in patients with anemia

was numerically lower compared with the increase in Hb in patients without anemia (p = 0.0007 [treatment-by-subgroup interaction at week 24]; Fig. 1A).

Treatment with dapagliflozin resulted in a decrease in the percentage of patients with anemia from 13% at baseline to 8% at week 24 (Supplementary Fig. 2). Hence, more patients treated with dapagliflozin achieved correction of anemia at the end of week 24 (52%) compared with those receiving placebo (26%). Thus, the difference in the proportion of patients who had anemia at baseline but had no anemia at week 24 was 26% (95% CI: 19.1, 33.4; Fig. 1B) between patients treated with dapagliflozin and those treated with placebo. In the group with no anemia at baseline, the incidence of new-onset anemia at week 24 was lower in patients treated with dapagliflozin (2.3%) versus those treated with placebo (6.5%; difference from placebo of −4.2; 95% CI: −5.4, −3.0; Fig. 1C).

3.3 Effect of dapagliflozin on serum albumin and body weight

Treatment with dapagliflozin resulted in a similar initial increase in serum albumin at week 4 in both patients with and without anemia, which remained stable thereafter until week 24 (Fig 2A). The adjusted mean changes from baseline at week 24 were 0.11 g/dL (95% CI: 0.07, 0.16) for dapagliflozin and 0.05 g/dL (95% CI: 0.01, 0.09) for placebo in patients with anemia. In patients with no anemia, the adjusted mean changes in serum albumin from baseline at week 24 were 0.04 g/dL (95% CI: 0.03, 0.06) and −0.02 g/dL (95% CI: −0.03, −0.01) for treatment with dapagliflozin and placebo, respectively. The placebo-adjusted mean changes in serum albumin upon treatment with dapagliflozin at week 24 were 0.06 g/dL (95% CI: 0.02, 0.10) for patients with anemia and 0.06 g/dL (95% CI: 0.05, 0.08) for patients with no anemia (p = 0.9746 [treatment-by-subgroup interaction at week 24]).

Patients in both the anemia and no-anemia groups showed a similar decrease in body weight upon treatment with dapagliflozin (p = 0.8275 [treatment-by-subgroup interaction at week 24]; Fig. 2B). The adjusted mean changes in body weight from baseline at week 24 in

the anemia group were −1.98 kg (95% CI: −2.46, −1.51) and −0.12 kg (95% CI: −0.60, 0.37) with dapagliflozin and placebo, respectively. The placebo-adjusted mean change in body weight upon treatment with dapagliflozin at week 24 was −1.87 kg (95% CI: −2.43, −1.30). The adjusted mean changes in body weight from baseline at week 24 in the no-anemia group were −2.18 kg (95% CI: −2.31, −2.04) and −0.27 kg (95% CI: −0.41, −0.14) with dapagliflozin and placebo, respectively. The placebo-adjusted mean change in body weight upon treatment with dapagliflozin at week 24 was −1.90 kg (95% CI: −2.09, −1.72).

3.4 Effect of dapagliflozin on SBP and eGFR

Patients in both the anemia and no-anemia groups showed a decrease in SBP at week 4 upon treatment with dapagliflozin (Fig. 2C), which then remained stable until week 24 (p = 0.7673 [treatment-by-subgroup interaction at week 24]). In the anemia group, the adjusted mean changes in SBP from baseline at week 24 were −6.27 mm Hg (95% CI: −8.27, −4.27) and −2.97 mm Hg (95% CI: −5.02, −0.93) upon treatment with dapagliflozin and placebo, respectively. The placebo-adjusted mean change in SBP upon treatment with dapagliflozin at week 24 was −3.29 mm Hg (95% CI: −5.45, −1.13). The adjusted mean changes in SBP from baseline at week 24 in the no-anemia group were −3.71 mm Hg (95% CI: −4.23, −3.18) and −0.76 mm Hg (95% CI: −1.29, −0.22) upon treatment with dapagliflozin and placebo, respectively. The placebo-adjusted mean change in SBP upon treatment with dapagliflozin at week 24 was −2.95 mm Hg (95% CI: −3.66, −2.24).

Treatment of patients in the anemia and no-anemia groups with dapagliflozin resulted in an initial decrease in eGFR at week 4, which then remained stable until week 24 (Fig. 2D). The adjusted mean changes in eGFR from baseline at week 24 in the anemia group were −0.76 mL/min/1.73 m^2 (95% CI: −2.39, 0.86) and 1.25 mL/min/1.73 m^2 (95% CI: −0.40, 2.91) upon treatment with dapagliflozin and placebo, respectively. The placebo-adjusted mean change in eGFR upon treatment with dapagliflozin at week 24 was −2.02 mL/min/1.73

m^2 (95% CI: −3.83, −0.20). The adjusted mean changes in eGFR from baseline at week 24 in the no-anemia group were −1.96 mL/min/1.73 m^2 (95% CI: −2.44, −1.49) and −1.07 mL/min/1.73 m^2 (95% CI: −1.56, −0.58) upon treatment with dapagliflozin and placebo, respectively. The placebo-adjusted mean change in eGFR upon treatment with dapagliflozin at week 24 was −0.89 mL/min/1.73 m^2 (95% CI: −1.54, −0.24). The decrease in eGFR upon treatment with dapagliflozin was similar in patients with and without anemia (p = 0.2536 [treatment-by-subgroup interaction at week 24]).

3.5 Adverse events

AEs were more common in patients with anemia (62.1%) than in patients without anemia (57.1%). In patients with anemia, AEs were observed in 64.2% (n = 228/355) of patients treated with dapagliflozin versus 59.9% (n = 209/349) of patients treated with placebo and SAEs were observed in 10.1% (n = 36/355) and 8.0% (n = 28/349) of patients in the dapagliflozin and placebo groups, respectively (Table 2). In the anemia group, 23 patients (6.5%) treated with dapagliflozin and 14 patients (4%) treated with placebo showed AEs with symptoms suggestive of renal impairment (Supplementary Table 2). AEs with symptoms suggestive of urinary tract infection were seen in 11 patients (3.1%) treated with dapagliflozin versus 17 patients (4.9%) treated with placebo. Additionally, AEs with symptoms suggestive of volume depletion were observed in 12 patients (3.4%) treated with dapagliflozin versus 3 patients (0.9%) treated with placebo.

Overall, 182 patients (7%) treated with dapagliflozin developed polycythemia at week 24 as compared with 31 patients (1%) treated with placebo (Supplementary Fig. 3). The mean (minimum/maximum) Hb values at week 24 last observation carried forward (LOCF) in patients who developed polycythemia at week 24 were 16.9 (16.1/18.8) g/dL in patients treated with dapagliflozin and 17.1 (16.1/19.8) g/dL in patients treated with placebo (Supplementary Table 3).

4. Discussion

This *post hoc* analysis investigated the effects of dapagliflozin in patients with T2D with and without anemia. Already at week 4 an increase in Hb was observed in patients treated with dapagliflozin, which gradually further increased to at least week 8 and was thereafter sustained throughout the follow-up period. This is similar to results from the EMPA-REG OUTCOME trial, showing a sustained increase in Hb by 0.6-0.8 mg/dL over 164 weeks of treatment with empagliflozin.[19] Furthermore, treatment with dapagliflozin corrected and prevented anemia in some patients. Overall, dapagliflozin was well tolerated in patients with or without anemia.

At the end of week 24, treatment with dapagliflozin of patients who had anemia at baseline was associated with correction of anemia in 52% of patients as compared with 26% of patients treated with placebo. Further, in patients with no anemia at baseline, the proportion of patients with incident anemia at week 24 was lower among patients treated with dapagliflozin, which suggested that dapagliflozin may have had a protective effect against the development of anemia in this patient group.

The increase in Hb during the first 4 weeks of treatment with dapagliflozin could be attributed to the small contraction in plasma volume exerted by the mild diuretic effect of dapagliflozin,[14,20] and is consistent with the increase in serum albumin and the decrease in SBP over the same period. This is in line with the mild increase in serum albumin that has been observed during the first week after SGLT2 inhibition without further increase thereafter.[21] However, the increase in Hb observed beyond week 4 indicates that stimulation of erythropoiesis rather than hemoconcentration is involved.[18,22,23]

The causes of anemia in this study are unknown but CKD is likely to be a contributing factor, as patients with anemia had a lower eGFR; hence, factors involved in the pathogenesis of renal anemia may be the underlying cause of anemia in this population. Contraction in

plasma volume seems to be similar in all patients, as the increase in Hb and serum albumin was comparable in patients with and without anemia during the first 4 weeks of treatment. The stimulation of erythropoiesis with dapagliflozin beyond week 8 seems to be weaker in patients with anemia. The etiology of renal anemia in patients with CKD is complex and multifactorial[24] and SGLT2i may have a limited effect on these mechanisms.

Several potential mechanisms beyond hemoconcentration could explain the sustained increase in Hb following dapagliflozin treatment. Studies have demonstrated that in patients with T2D, administration of SGLT2i is associated with increases in serum erythropoietin concentration until this peaks at 2-4 weeks after the start of treatment.[14, 25, 26] It has been proposed that in patients with T2D, SGLT2i reduces the workload of the proximal tubules, which leads to a decrease in tubulointerstitial hypoxia, resulting in a reversal of the hypoxia-induced injury caused to "neural crest derived" fibroblasts, which in turn enables these cells to once again produce erythropoietin.[22] Thus, beyond week 4, the longer-term increase in Hb in response to dapagliflozin treatment can be possibly attributed to the generation and release of erythropoietin by the kidneys.

Another potential mechanism that could explain the increase in Hb levels upon treatment with dapagliflozin is the stimulation of the synthesis and release of arginine vasopressin (AVP) triggered by the reduction in plasma volume caused by the diuretic effect of dapagliflozin.[20] Treatment of patients with T2D with dapagliflozin has been shown to induce a small but significant increase in circulating copeptin, a surrogate marker for AVP.[20] As AVP has been demonstrated in experimental anemia settings to rapidly increase red blood cell count and stimulate erythropoiesis in an erythropoietin-independent manner,[23] AVP-dependent mechanisms could explain, at least in part, the increases in Hb with dapagliflozin treatment.

Patients with anemia were older and had T2D for a longer duration, and there was also a higher proportion of blacks/African Americans in this group. They also had a lower mean eGFR and a higher UACR compared with patients without anemia. This was expected, given the known correlation between the incidence of anemia and factors such as age, duration of T2D, and CKD.[27,28] Average levels of Hb, hematocrit, and mean corpuscular volume have been found to be lower in African Americans compared with whites.[29] Analysis of the baseline characteristics also demonstrated that 28% of patients with eGFR <60 mL/min/1.73 m^2 had anemia compared with 9% of patients with eGFR ≥60 mL/min/1.73 m^2. A similar correlation between advanced CKD and anemia in patients with T2D has been demonstrated in other studies.[2,30]

Dapagliflozin was generally well tolerated, with the proportion of patients with AEs being slightly higher in the anemia group versus the no-anemia group. This could be because of the lower mean eGFR and longer duration of T2D at baseline in patients with anemia versus those without anemia. Mild polycythemia developed in 7% of patients treated with dapagliflozin and 1% of patients treated with placebo. This mild polycythemia has not been found to pose a risk of blood clots leading to heart attacks or stroke.[31,32] Instead, treatment with SGLT2i has been shown to lead to a decrease in the risk of cardiovascular events in patients with T2D with or without CKD.[33-36] An exploratory mediation analysis of the time-dynamic evolution of the potential mediators and the outcome of cardiovascular death of the EMPA-REG OUTCOME trial demonstrated that changes in hematocrit and Hb mediated 51.8% and 48.9%, respectively, of the effect of empagliflozin on the reduction in the risk of cardiovascular death in patients with T2D and established CVD;[19] similar results were shown in a mediation analysis from the CANVAS Program in patients with T2D and heart failure.[37] An initial increase in hematocrit with empagliflozin followed by stabilization from baseline to week 164 was observed compared with no notable change in the placebo group.[19]

Dapagliflozin, in addition to its antiglycemic effect, could play a cardio-protective role by a diversity of other mechanisms, including its effect on Hb concentration. Since anemia is also an independent risk factor for rapid CKD progression,[4] improved Hb levels may contribute to the SGLT2i benefit on kidney function decline.

A strength of this analysis is that pooled data were used, providing an overview of a large patient population. A limitation, however, was that some of the endpoints were not included in the original studies. Data on serum erythropoiesis markers, such as iron, ferritin, transferrin, hepcidin, and reticulocytes, were also not available.

5. Conclusions

In conclusion, treatment with dapagliflozin resulted in clinically meaningful increases in Hb concentration in patients with T2D and resulted in correction and prevention of anemia. The mechanism may be a combination of hemoconcentration due to a diuretic effect (early phase) and increased erythropoiesis (late phase). Further studies would be required to elucidate the mechanisms by which dapagliflozin increases and maintains Hb at a higher level in patients with T2D.

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Declarations of interest

B.V.S., C.D.S., P.J.G., and P.S. are employees and shareholders of AstraZeneca. H.J.L.H. is a consultant to AbbVie, Astellas, AstraZeneca, Boehringer Ingelheim, Janssen, and ZS-Pharma (honoraria were paid to his employer). D.C.W. has received consultancy fees or honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Napp, Mundipharma, Pharmacosmos, Reata, and Vifor Fresenius. V.C. is a former employee of AstraZeneca and owns AstraZeneca stock. R.C.R. has received honoraria from AbbVie, AstraZeneca, GlaxoSmithKline, and Boehringer Ingelheim, and has lectured for Amgen, Janssen, Takeda, AstraZeneca, Boehringer Ingelheim, and Roche.

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Author contributions

B.V.S., C.D.S., P.J.G., P.S., H.J.L.H., D.C.W., V.C., and R.C.R. made substantial contributions to the conception and design of the study, acquisition of data, or analysis and

interpretation of data; drafted the article and revised it critically for important intellectual content; and gave final approval to the version submitted for publication.

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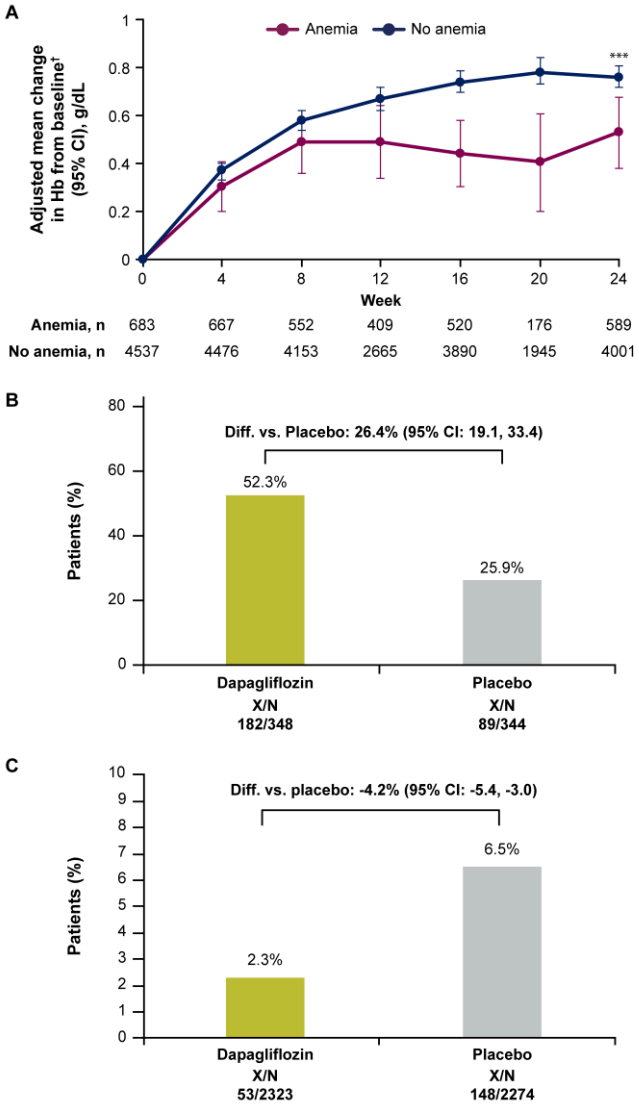
Figure Legends

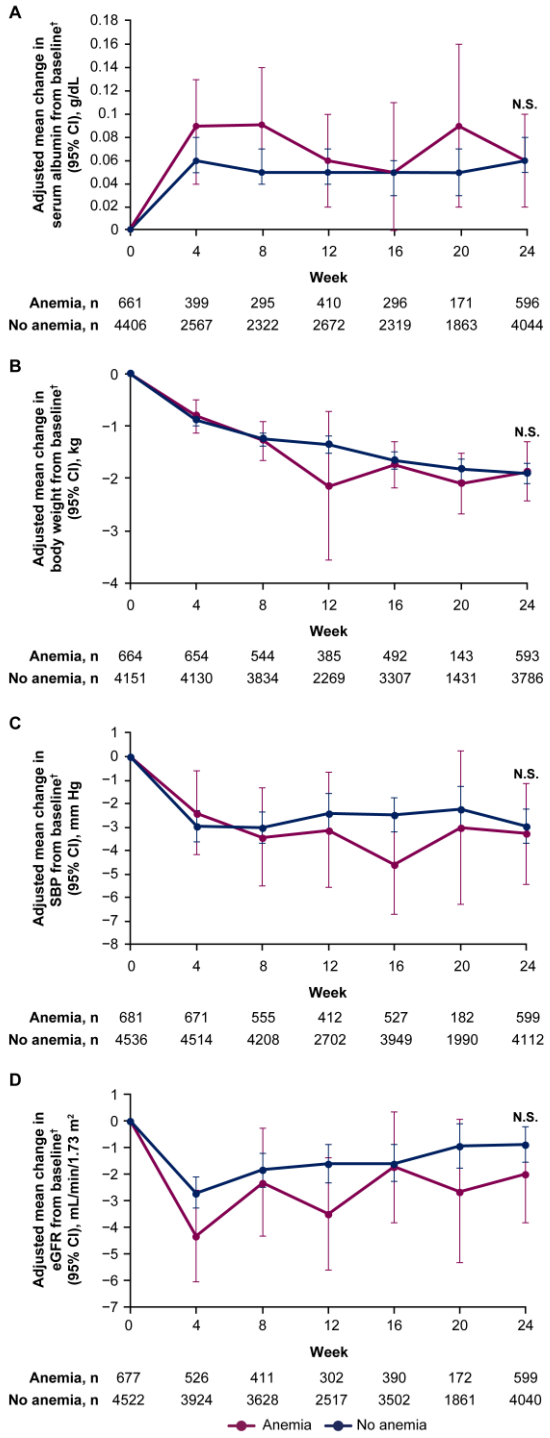
Fig 1. (A) Placebo-adjusted mean change in Hb from baseline to week 24 upon treatment with dapagliflozin in patients with T2D with and without anemia, (B) proportion of patients with anemia at baseline who had no anemia at week 24 upon treatment with dapagliflozin and placebo, (C) incidence of anemia at week 24 in patients with no anemia at baseline upon treatment with dapagliflozin and placebo



***p-value for treatment-by-subgroup interaction at week 24 <0.001. †Difference versus placebo

CI, confidence interval; Diff., difference; Hb, hemoglobin; N, total number of patients; T2D, type 2 diabetes; X, number of patients who had anemia at baseline but no anemia at week 24

Fig 2. Placebo-adjusted mean changes from baseline to week 24 in (A) serum albumin, (B), body weight (C), systolic blood pressure, and (D) eGFR upon treatment with dapagliflozin in patients with T2D with and without anemia



†Difference versus placebo

CI, confidence interval; eGFR, estimated glomerular filtration rate; N.S., not significant i.e. p-value for treatment-by-subgroup interaction at week 24 >0.1; SBP, systolic blood pressure; T2D, type 2 diabetes

Table 1. Baseline demographics and characteristics

	Anemia[†]		No anemia[‡]	
	Placebo N = 348	**Dapagliflozin N = 352**	**Placebo N = 2286**	**Dapagliflozin N = 2339**
Age, years, mean (SD)	62.9 (9.49)	62.6 (9.39)	59.7 (9.87)	59.0 (10.00)
Male, n (%)	209 (60.1)	208 (59.1)	1340 (58.6)	1360 (58.1)
Race, n (%)				
White	251 (72.1)	259 (73.6)	1874 (82.0)	1906 (81.5)
Asian	46 (13.2)	44 (12.5)	259 (11.3)	273 (11.7)
Black/African American	32 (9.2)	37 (10.5)	60 (2.6)	62 (2.7)
Other[a]	19 (5.5)	12 (3.4)	93 (4.1)	98 (4.2)
Weight, kg, mean (SD)	89.7 (21.97)	92.5 (23.19)	89.2 (18.96)	89.7 (19.03)
SBP, mm Hg, mean (SD)	134.5[b] (16.26)	133.2 (16.20)	131.9 (15.07)	132.0 (15.35)
Bicarbonate, mEq/L, mean (SD)	23.6 (3.32)	24.3 (3.44)	25.1[c] (2.85)	25.1[d] (2.90)
Hct (%), mean (SD)	35.7 (2.43)	35.8 (2.50)	42.9[e] (3.54)	42.8[f] (3.52)
Hb, g/dL, mean (SD)	11.8 (0.80)	11.8 (0.78)	14.3 (1.18)	14.3 (1.16)
Median	11.9	11.8	14.3	14.2
Min,max	8.9, 12.9	8.2, 12.9	12.0, 18.8	12.0, 18.8
Duration of T2D, years, mean (SD)	13.9 (9.29)	14.8 (9.52)	9.3[c] (8.23)	9.3 (8.10)
HbA_{1c}, %, mean (SD)	8.2 (1.04)	8.2 (0.87)	8.2 (0.98)	8.2 (0.98)
UACR, mg/g, mean (SD)	306.0 (751.45)	240.4[g] (504.70)	91.8[c] (345.78)	86.1[f] (308.74)
UACR, mg/g, median	32.7	29.0[g]	12.0[c]	11.0[f]
eGFR mL/min/1.73 m^2, mean (SD)	65.9 (24.73)	66.6 (22.70)	78.3[c] (20.41)	78.9 (20.56)
eGFR categorization, mL/min/1.73 m^2, n (%)				
<30	6 (1.7)	4 (1.1)	7[c] (0.3)	4 (0.2)
≥30 to <45	63 (18.1)	60 (17.0)	90[c] (3.9)	101 (4.3)
≥45 to <60	103 (29.6)	88 (25.0)	323[c] (14.1)	319 (13.6)
≥60 to <90	111 (31.9)	137 (38.9)	1229[c] (53.8)	1227 (52.5)
≥90	65 (18.7)	63 (17.9)	636[c] (27.8)	688 (29.4)
History of CVD and/or HF[h], %	41.1	46.0	44.1	43.1
History of hypertension[h], %	56.0	64.8	71.6	68.5
History of PVD/PAD[h], %	8.3	13.4	11.9	11.4
ACEi and/or ARB, %	82.8	85.2	70.3	68.1
Diuretics, %	37.4	39.5	25.1	20.6
Iron supplementation, %	7.2	6.0	0.8	1.0
ESA, %	0.3	0.0	0.0	0.0

[†]Defined by World Health Organization as Hb <13 g/dL in men and <12 g/dL in women
[‡]Defined by World Health Organization as Hb ≥13 g/dL in men and ≥12 g/dL in women
[a]The race subgroup of other includes patients with reported race of American Indian/Alaska Native, Native Hawaiian/other Pacific Islander, or Other

[b]N = 347
[c]N = 2285
[d]N = 2338
[e]N = 2284
[f]N = 2337
[g]N = 351
[h]Disease history was not available for 2 of the 14 trials

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; HbA_{1c}, glycated hemoglobin; Hct, hematocrit; HF, heart failure; N, number of patients; PAD, peripheral artery disease; PVD, peripheral vascular disease; SBP, systolic blood pressure; SD, standard deviation; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

Table 2. Summary of adverse events[†] and adverse events in system organ classes of interest (safety analysis set[‡])

	Anemia		**No anemia**	
	Placebo	Dapagliflozin	Placebo	Dapagliflozin
N	349	355	2294	2353
At least one AE, n (%)	209 (59.9)	228 (64.2)	1275 (55.6)	1377 (58.5)
At least one SAE, n (%)	28 (8.0)	36 (10.1)	134 (5.8)	115 (4.9)
Deaths, n (%)	0	1 (0.3)	6 (0.3)	8 (0.3)
Any AE in SOCs of interest	68 (19.5)	65 (18.3)	309 (13.5)	341 (14.5)
Blood and lymphatic system disorders, n (%)	23 (6.6)	12 (3.4)	21 (0.9)	12 (0.5)
Cardiac disorders, n (%)	17 (4.9)	14 (3.9)	90 (3.9)	73 (3.1)
Vascular disorders, n (%)	15 (4.3)	18 (5.1)	113 (4.9)	96 (4.1)
Renal and urinary disorders, n (%)	24 (6.9)	32 (9.0)	111 (4.8)	199 (8.5)

[†]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 short-term double-blind treatment plus 4 days/30 days or up to and including the start date of the long-term period or up to the follow-up visit if earlier.

[‡]Safety analysis set includes patients who received at least 1 dose of study drug

Adverse events were classified as per MedDRA version 17.1

AE, adverse event; SOC, system organ class; SAE, serious adverse event

Supplementary Material

Supplementary Table 1. Dapagliflozin clinical trials included in the pooled analysis (Details TBC)

Study Name (ClinicalTrials.gov identifier)	Phase 2/3	Title	Treatment arms	Treatment duration
MB102-013 (NCT)				
MB102-014 (NCT)				
MB102-029 (CKD) (NCT)				
MB102-030 (NCT)				
MB102-034 (NCT)				
D1690C00005 (NCT)				
D1690C00006 (NCT)				
D1690C00010 (NCT)				
D1690C00012 (NCT)				
D1690C00018 (NCT)				
D1690C00019 (NCT)				
D1690C00023 (DELIGHT) (NCT)				
D1690C00024 (DERIVE) (NCT)				
D1692C00006 (Japan) (NCT)				

CKD, chronic kidney disease

Supplementary Table 2. Adverse events[†] suggestive of renal impairment[a], urinary tract infection[b] and volume depletion[c] (safety analysis set[‡])

	Anemia		No-anemia	
	Placebo	Dapagliflozin	Placebo	Dapagliflozin
N	349	355	2294	2353
Patients with any AE with symptoms suggestive of renal impairment, n (%)[a]	14 (4.0)	23 (6.5)	40 (1.7)	67 (2.8)
Renal impairment	2 (0.6)	7 (2.0)	14 (0.6)	17 (0.7)
Creatinine renal clearance decreased	3 (0.9)	6 (1.7)	13 (0.6)	21 (0.9)
Creatinine renal clearance abnormal	-	-	1 (<0.1)	1 (<0.1)
Blood creatinine increased	2 (0.6)	1 (0.3)	9 (0.4)	17 (0.7)
Renal failure	0	3 (0.8)	2 (<0.1)	1 (<0.1)
Acute kidney injury	3 (0.9)	2 (0.6)	0	5 (0.2)
Glomerular filtration rate decreased	2 (0.6)	2 (0.6)	3 (0.1)	7 (0.3)
Chronic kidney disease	0	1 (0.3)	-	-
Renal function test abnormal	0	1 (0.3)	-	-
Cystatin C increased	1 (0.3)	0	0	2 (<0.1)
Urine output decreased	1 (0.3)	0	1 (<0.1)	0
Urine flow decreased	-	-	0	1 (<0.1)
Patients with any AE with symptoms suggestive of urinary tract infection, n (%)[b]	17 (4.9)	11 (3.1)	77 (3.4)	105 (4.5)
Urinary tract infection	14 (4.0)	11 (3.1)	57 (2.5)	86 (3.7)
Cystitis	3 (0.9)	0	15 (0.7)	15 (0.6)
Escherichia urinary tract infection	-	-	0	1 (<0.1)
Genitourinary tract infection	-	-	0	1 (<0.1)
Prostatitis	-	-	3 (0.1)	1 (<0.1)
Pyelonephritis	-	-	1 (<0.1)	1 (<0.1)
Trigonitis	-	-	0	1 (<0.1)
Urethritis	-	-	1 (<0.1)	1 (<0.1)
Kidney infection	-	-	1 (<0.1)	0
Patients with any AE with symptoms suggestive of volume depletion, n (%)[c]	3 (0.9)	12 (3.4)	20 (0.9)	30 (1.3)
Hypotension	0	7 (2.0)	5 (0.2)	16 (0.7)
Syncope	1 (0.3)	4 (1.1)	3 (0.1)	6 (0.3)
Orthostatic hypotension	1 (0.3)	1 (0.3)	8 (0.3)	4 (0.2)
Dehydration	1 (0.3)	0	0	3 (0.1)
Urine output decreased	1 (0.3)	0	1 (<0.1)	0
Blood pressure decreased	-	-	2 (<0.1)	1 (<0.1)
Urine flow decreased	-	-	0	1 (<0.1)

Circulatory collapse	-	-	1 (<0.1)	0

† 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 short-term double-blind treatment plus 4 days/30 days or up to and including the start date of the long-term period or up to the follow-up visit if earlier

‡ Safety analysis set includes patients who received at least one dose of study drug

[a]Based on a predefined list of preferred terms of renal impairment

[b]Based on a predefined list of preferred terms of urinary tract infection

[c]Based on a predefined list of preferred terms of volume depletion

Adverse events were classified as per MedDRA version 17.1

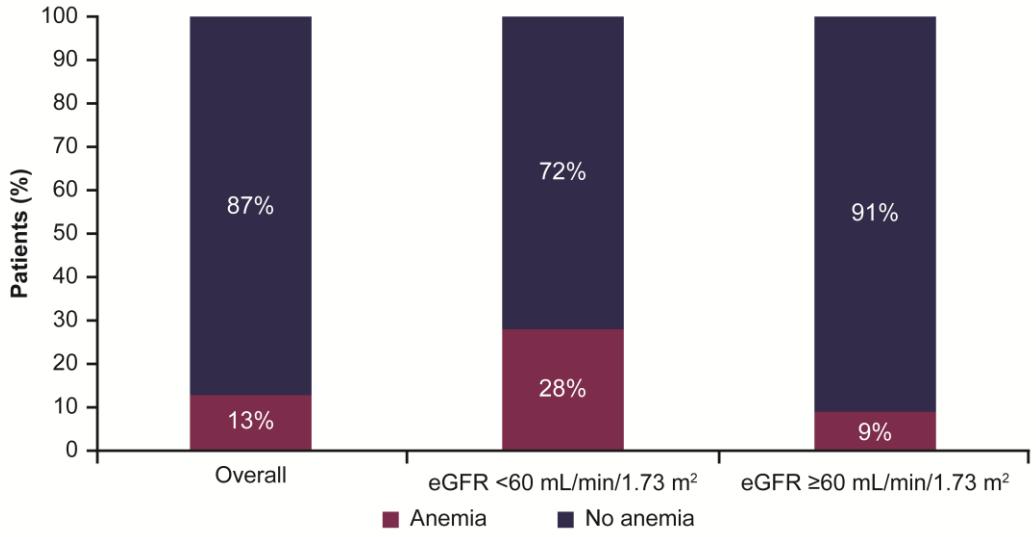
Supplementary Table 3. Hemoglobin concentration at baseline and week 24 in patients with no-anemia at baseline who developed polycythemia at week 24 upon treatment with dapagliflozin and placebo

			Hemoglobin (g/dL)		
	Timepoint	N	Mean (SD)	Min	Max
Placebo	Baseline	31	15.7 (0.8)	13.2	16.5
	Week 24	31	17.1 (0.7)	16.1	19.8
Dapagliflozin	Baseline	182	15.6 (0.6)	13.1	16.5
	Week 24	182	16.9 (0.5)	16.1	18.8

Max, maximum; Min, minimum, N, number of patients; SD, standard deviation

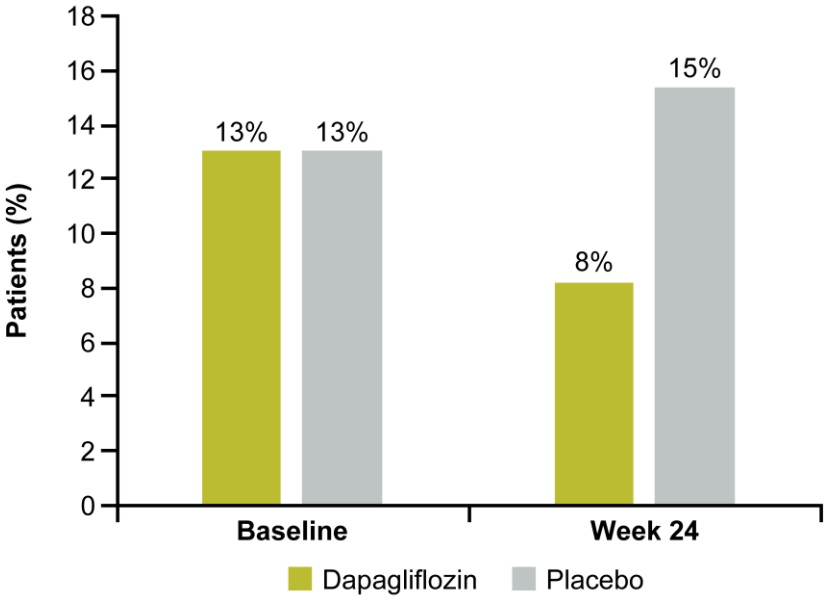
Supplementary Figure Legends

Supplementary Fig. 1. Proportion of patients with and without baseline CKD (eGFR <60 mL/min/1.73 m^2) relative to anemia at baseline

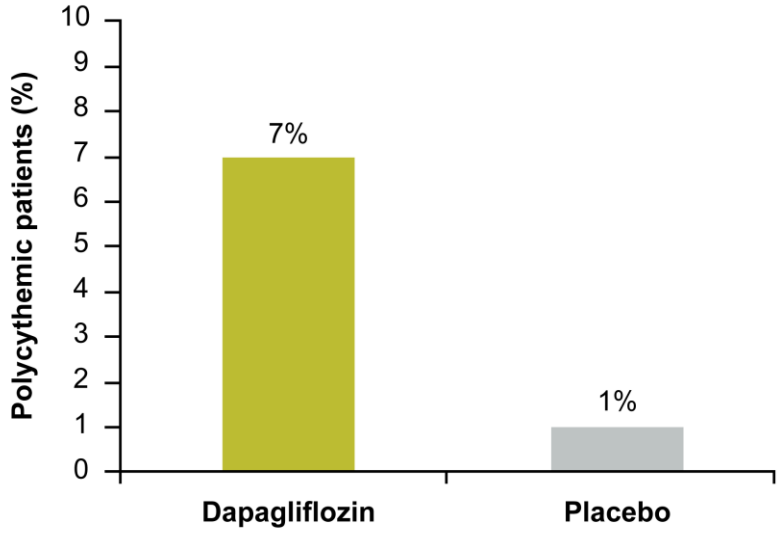


CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

Supplementary Fig. 2. Percentage of patients with anemia at baseline and week 24 after treatment with dapagliflozin and placebo



Supplementary Fig. 3. Percentage of patients from both anemia and no-anemia groups who developed polycythemia[†] at week 24 LOCF upon treatment with dapagliflozin and placebo



[†]Hb >16.5 g/dL in men and >16 g/dL in women

Hb, hemoglobin; LOCF, last observation carried forward