Health-Related Quality-of-Life Analysis for Patients With Type 2 Diabetes Mellitus Treated With Empagliflozin

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BACKGROUND

- Type 2 diabetes mellitus (T2DM) is characterized by high blood glucose levels caused by an increase in insulin resistance and a progressive decrease in the ability of the beta cells in the pancreas to produce sufficient amounts of insulin to control blood glucose.
- T2DM can lead to macrovascular complications, such as coronary heart disease and stroke, and/or microvascular complications, such as renal failure, retinopathy, and neuropathy.
- Disease progression may also impact health-related quality of life (HRQOL) and health care resource utilization (HCRU).
- Empagliflozin is an oral antidiabetic drug that selectively inhibits the sodium-glucose cotransporter 2 and increases urinary glucose excretion by blocking glucose reabsorption by the kidney.
- Treatment with empagliflozin results in clinically meaningful reductions in HbA1c, systolic blood pressure, and body weight, and demonstrates good overall safety and tolerability in patients with T2DM.[1,2,3]

OBJECTIVE

- To evaluate the effect of empagliflozin on HRQOL using the EuroQOL-5 dimensions questionnaire (EQ-5D) and HCRU.

METHODS

- Six phase 3 clinical trials of empagliflozin in T2DM have assessed efficacy, safety, and health outcomes of empagliflozin as monotherapy or in combination with other oral antidiabetic treatments (Table 1).

Table 1. *Antidiabetic Treatment Studies*

Trial	Empa Dosage	Background Therapy	Control(s)	Duration (Weeks)	Time Points (Weeks)
EMPA-REG PIO	10 mg and 25 mg	Pioglitazone ± metformin	Placebo	24	6, 12, 24
EMPA-REG MONO	10 mg and 25 mg	None	Placebo Sitagliptin 100 mg	24	6, 12, 24
EMPA-REG MET	10 mg and 25 mg	Metformin	Placebo	24	6, 12, 24
EMPA-REG METSU	10 mg and 25 mg	Metformin + sulfonylurea	Placebo	24	6, 12, 24
EMPA-REG H2H-SU	25 mg	Metformin	Glimepiride 1-4 mg	104	8, 28, 52, 78, 104
EMPA-REG RENAL	10 mg and 25 mg	Pre-existing therapy	Placebo	52	6, 12, 24, 52
EMPA-REG MDI	10 mg and 25 mg	Insulin ± metformin	Placebo	52	4, 18, 24, 40, 52

Empa = Empagliflozin.

Note 1: Studies EMPA-REG MET and EMPA-REG METSU were regarded as independent substudies of the clinical trial, in which patients were recruited and randomized within the metformin or metformin plus sulfonylurea background medications, respectively.

Note 2: The randomization of patients in trial EMPA-REG RENAL was stratified by the level of renal impairment (mild, moderate, and severe). Empagliflozin 10 mg was not investigated in patients with moderate or severe renal impairment in this trial.

Patient Population

- The patient population in each trial consisted of patients aged 18 years and older with T2DM with insufficient glycemic control (HbA1c ≥ 7% and ≤ 10%). BMI was ≤ 45 kg/m^2 in trials EMPA-REG H2H-SU and EMPA-REG RENAL and 30 kg/m^2-45 kg/m^2 in trial EMPA-REG MDI. Trial EMPA-REG RENAL enrolled only patients with renal impairment: mild (epidermal growth factor receptor [eGFR] from 60 to < 90), moderate (eGFR 30 to < 60), and severe (eGFR 15 to < 30).

Endpoints

EQ-5D Utility Index

- HRQOL was obtained from the EQ-5D questionnaire, which assesses the health of a respondent on a scale of 1 to 3 (1 = no problems, 2 = some problems, 3 = extreme problems) across five dimensions (mobility, self-care, usual activity, pain or discomfort, and anxiety or depression).
- The possible health states for each respondent are converted into a single utility index score through time trade-off techniques[4] using the United Kingdom tariffs (1 represents perfect health and 0 represents death, but negative scores are possible).

EQ-5D VAS

- Patient overall self-rated health status was obtained from the EQ-5D visual analog scale (VAS).
- The EQ-5D VAS asks respondents to rate their present health status on a visual scale from 0 to 100, with 0 labeled as "Worst imaginable health state" and 100 labeled as "Best imaginable health state."

HCRU

- During the randomized treatment period, HCRU data were collected for the following health care resources: emergency department visits, outpatient visits (i.e., general physician, specialist, nurse, dietician, chiropodist, and other), home visits, emergency room visits, hospitalizations (i.e., general ward, intensive care, and overnight emergency room visits), and days unable to work due to diabetes.
- Patients were asked to record whether HCRU was related to T2DM.

Analysis

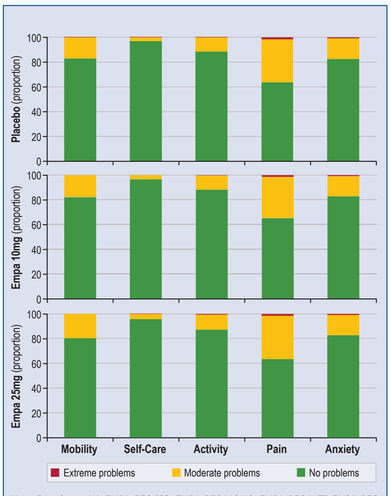
- The analysis populations for the EQ-5D utility index and the EQ-5D VAS consisted of all patients in the full analysis set* in each trial with a baseline and at least one post-baseline EQ-5D utility index measurement and EQ-5D VAS measurement, respectively. The analysis population for HCRU was all patients in the full analysis set in each trial.
- The EQ-5D utility index and EQ-5D VAS were summarized by visit and treatment arm for each trial and pooled across trials (according to randomized treatments).
- Overall, diabetes-related, and non–diabetes-related HCRU was pooled across trials and summarized over the first 24 weeks of treatment.
- Active controls and open-label arms were excluded from the pooled analysis.
- Linear mixed models for repeated measures up to 24 weeks were implemented with EQ-5D change from baseline in utility index and VAS score as outcomes. Results at week 24 are presented as adjusted least squares mean changes from baseline for each treatment and for differences between treatments.
  - Study, time since baseline (continuous), and treatment were evaluated as main effects and all two- and three-way interaction terms. Random intercept and slope were included to capture within-patient correlation.
  - A backward selection process with a p value ≤ 0.10 was used to identify baseline covariates (see Table 2) associated with an outcome. A slightly relaxed p value was used (i.e., 0.10 instead of 0.05), due to the exploratory nature of the analysis.

* The full analysis set comprised all randomized patients treated with at least one dose of the study drug and with a baseline glycated hemoglobin (HbA1c) measurement.

RESULTS

EQ-5D Utility Index

- The overall completion rate of the EQ-5D utility index in all treatment arms up to 24 weeks (up to 28 weeks for trial EMPA-REG H2H-SU) was 90% or above in each trial (87% for placebo arm in trial EMPA-REG MONO).
- Baseline distribution of the EQ-5D responses (i.e., dimensions) was similar between placebo and empagliflozin groups.
  - The most commonly reported problem was pain/discomfort; the percentage of patients reporting at least a moderate level of pain/discomfort ranged from 21% to 57% across the trials (Figure 1).



Note: Data from trials EMPA-REG PIO, EMPA-REG MONO, EMPA-REG MET, EMPA-REG METSU, EMPA-REG RENAL, and EMPA-REG MDI were included in the pooled analysis.

- The observed mean EQ-5D utility index at baseline was comparable across the trials and ≥ 0.79, which indicates a high baseline patient utility.
- The observed mean EQ-5D utility index varied only slightly across all trials at post-baseline visits, without a clear trend, and there were no notable differences between the empagliflozin treatment arms and the placebo arm.
- For the multivariable modeling selection, the adjustment factors that had an effect on the EQ-5D utility index and EQ-5D VAS are presented in Table 2

Table 2. *Inclusion and Significance of Factors In Adjusted Multivariable Models*

Factor	EQ-5D Index Score	EQ-5D VAS Score
Study	√[a]	NS
Treatment	NS	√[a]
Time	NS	√[a]
Study-by-treatment interaction	NS	NS
Study-by-time interaction	√[a]	NS
Treatment-by-time interaction	NS	NS
Study-by-treatment-by-time interaction	NS	NS
Baseline covariates		
Baseline value	√[a]	√[a]
eGFR	√[a]	NI
Sex	√[a]	NI
Race	√[a]	√[a]
Country	√[a]	√[a]
Age	√[a]	√[a]
Systolic blood pressure	√[b]	NI
Diastolic blood pressure	NI	NI
BMI	√[a]	√[a]
Time since diagnosis	NI	√[b]
Cardiovascular risk predictor	√[a]	NI
Prior cardiovascular risk	NI	NI

√ = significant; BMI = body mass index; eGFR = estimated glomerular filtration rate; NI = not included; NS = not significant.

[a] p ≤ 0.05; [b] 0.05 < p ≤ 0.1.

- Table 3 presents the adjusted least squares mean change from the baseline EQ-5D utility index estimates.
  - Within treatment groups: positive and significantly different from zero in three studies: empagliflozin 25 mg in study EMPA-REG PIO, empagliflozin 10 mg in study EMPA-REG METSU, placebo in study EMPA-REG MET; negative and significantly different from zero in empagliflozin 25 mg in study EMPA-REG MDI
  - Between treatment groups: positive and significantly different between empagliflozin 25 mg and placebo in study EMPA-REG RENAL
  - Pooled across trials: No significant differences between any empagliflozin treatment arm and placebo

Table 3. *Adjusted Least Squares Mean Change From Baseline in the EQ-5D Utility Index at 24 Weeks, by Trial*

Trial	Adjusted Least Squares Means[a]				
	Empa 25 mg	Empa 10 mg	Placebo	Difference Between Empa 25 mg and Placebo	Difference Between Empa 10 mg and Placebo
EMPA-REG PIO	0.026[b]	0.011	0.002	0.024	0.010
EMPA-REG MONO	0.018	0.015	0.015	0.002	−0.001
EMPA-REG MET	0.007	0.019	0.032[b]	−0.025	−0.013
EMPA-REG METSU	0.003	0.026[b]	0.017	−0.014	0.009
EMPA-REG RENAL	0.009	0.001	−0.017	0.026[b]	0.018
EMPA-REG MDI	−0.023[b]	−0.016	−0.009	−0.014	−0.007
Pooled across trials	0.007	0.010[b]	0.007	−0.000	0.003

[a] The model contained fixed effects for time, treatment, study, treatment by time, study by time, study by treatment, study by treatment by time, baseline EQ-5D utility index score, age, sex, race, BMI, country, systolic blood pressure, estimated eGFR at baseline, and cardiovascular risk predictor and random intercept and slope.

[b] p ≤ 0.05; no adjustments were made for multiple comparisons.

Note: Data from trials EMPA-REG PIO, EMPA-REG MONO, EMPA-REG MET, EMPA-REG METSU, EMPA-REG RENAL, and EMPA-REG MDI were included in the pooled analysis.

EQ-5D VAS

- Because the same PRO instrument was used to collect data for the EQ-5D utility index and the EQ-5D VAS, the completion rates were very similar.
- The observed mean EQ-5D VAS baseline values were above 70, indicating a high patient health state at baseline.
- In all trials, the observed mean EQ-5D VAS slightly increased over time in all treatment arms.
- Table 4 presents the adjusted least squares mean change from the baseline EQ-5D VAS estimates.
  - Within treatment groups: positive and significantly different from zero in all trials, except for the empagliflozin 25 mg and placebo treatment groups in study EMPA-REG MDI
  - Between treatment groups: positive and significantly different between empagliflozin 10 mg and placebo in study EMPA-REG MDI
  - Pooled across trials: Significantly different between both empagliflozin treatment arms and placebo

Table 4. *Adjusted Least Squares Mean Change From Baseline in the EQ-5D VAS Score at 24 Weeks, by Trial*

Trial	Adjusted Least Squares Means[a]				
	Empa 25 mg	Empa 10 mg	Placebo	Difference Between Empa 25 mg and Placebo	Difference Between Empa 10 mg and Placebo
EMPA-REG PIO	5.2[b]	3.6[b]	2.8[b]	2.4	0.8
EMPA-REG MONO	3.8[b]	3.8[b]	2.5[b]	1.3	1.3
EMPA-REG MET	2.7[b]	4.5[b]	3.8[b]	−1.1	0.7
EMPA-REG METSU	3.3[b]	4.2[b]	2.3[b]	1.0	1.9
EMPA-REG RENAL	3.4[b]	4.0[b]	1.4[b]	1.9	2.5
EMPA-REG MDI	0.8	3.9[b]	0.5	0.4	3.4[b]
Pooled across trials	3.2[b]	4.0[b]	2.2[b]	1.0[b]	1.8[b]

[a] The model contained fixed effects for time, treatment, study, treatment by time, study by time, study by treatment, study by treatment by time, baseline EQ-5D VAS, age, race, BMI, country, and time since diagnosis of T2DM (years), and random intercept and slope.

[b] p ≤ 0.05; no adjustments were made for multiple comparisons.

Note: Data from trials EMPA-REG PIO, EMPA-REG MONO, EMPA-REG MET, EMPA-REG METSU, EMPA-REG RENAL, and EMPA-REG MDI were included in the pooled analysis.

HCRU

Visits

- The largest percentages of visits were observed for visits to general physicians (15.0% of patients for empagliflozin 25 mg, 17.8% for empagliflozin 10 mg, and 15.4% for placebo) and specialists (10.3% for empagliflozin 25 mg, 11.2% for empagliflozin 10 mg, and 10.6% for placebo). Percentages of ≤ 1.3% were observed for visits to nurses, dieticians, and chiropodists and for home visits.
- Emergency room visits were relatively rare (3.5% for empagliflozin 25 mg and placebo, 2.5% for empagliflozin 10 mg); the average number of emergency room visits was similar for empagliflozin 25 mg (1.2 visits), empagliflozin 10 mg (1.1 visits), and placebo (1.1 visits).

Hospitalizations

- The percentage of patients who reported a general ward hospitalization was low and varied only slightly (2.3% for empagliflozin 25 mg, 2.6% for empagliflozin 10 mg, and 2.9% for placebo) across treatment arms.
  - For patients who were hospitalized, the average number of days in the general ward was similar for empagliflozin 25 mg (8.7 days), empagliflozin 10 mg (7.4 days), and placebo (9.4 days).
- The percentage of patients who reported being in intensive care was < 0.5% in all treatment arms.
- The percentage of patients who reported overnight emergency room stays was ≤ 0.5% in all treatment arms.

Days Unable to Work Due to Diabetes

- Among patients who reported that they were employed at least part-time at baseline, the percentage reporting that they missed work due to diabetes was < 0.5% in all treatment arms.

CONCLUSIONS

- Patient utility, measured by the EQ-5D utility index, and self-rated health status, measured by the EQ-5D VAS, at baseline were high for all treatment groups in each trial. Baseline distribution of the EQ-5D responses (i.e., dimensions) was similar between placebo and empagliflozin groups; the most commonly reported problem was pain/discomfort.
- Patient utility generally increased over time in all treatment arms, but changes were small due to little room left for improvement (i.e., ceiling effect); only three of the positive changes in patient utility were statistically significant.
- Similarly, self-rated health status generally increased over time in all treatment arms, but changes were small; all but two of the positive changes in self-rated health status were statistically significant.
- The multivariable analyses indicate that differences in patient utility and self-rated health status between empagliflozin, as a monotherapy or in combination with other antihyperglycemic treatment regimens, and placebo at 24 weeks were generally positive but small, and only a few were statistically significant.
- When pooled across trials, there were no significant differences between any empagliflozin treatment arm and placebo for the EQ-5D utility index; however, a significant but small benefit was observed in both empagliflozin treatment arms compared with placebo for the EQ-5D VAS.
- The percentage of patients who used any type of health care resource (i.e., diabetes-related or non–diabetes-related) during the treatment period was low and not statistically different between the empagliflozin and placebo treatment arms. The majority of the resources used were non–diabetes-related.
- The results of the analyses performed demonstrate that the high baseline patient utility and self-rated health status was maintained, and HCRU was low during the randomized treatment period in empagliflozin and placebo treatment groups.

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