**SUPPLEMENTAL MATERIAL**

# Effects of Semaglutide on Symptoms, Function, and Quality of Life in Patients with Heart Failure with Preserved Ejection Fraction and Obesity: A Prespecified Analysis of the STEP-HFpEF Trial

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**Additional information on the imputation methods to account for missing data**

The primary analysis was a multiple imputation similar to the one described by McEvoy et al and Wang et al (see the details in the section 2.1 of the publication by Wang et al).[32,33] A single imputation approach using an unfavorable value was employed for KCCQ-CSS when participants had missing measurements at week 52 due to CV death, or for those participants with a HF event prior to a missing measurement at week 52 (non-retrieved measurements). The unfavorable value was determined using the minimal value observed during the trial. For participants in the semaglutide and placebo groups, missing primary endpoint measurements at week 52 for non-retrieved participants were imputed using assessments from retrieved participants in each treatment group. This was done according to the timing and the actual value of last available observation during the on-treatment period for KCCQ-CSS and body weight. Furthermore, baseline BMI category, baseline body weight, baseline KCCQ-CSS (not for change in body weight) and sex were used in the imputation model. The imputation approach for other KCCQ domains was similar to that for KCCQ-CSS.

The statistical model and imputation approach for confirmatory secondary endpoints of change in CRP (log transformed) and 6MWD were the same as for the primary endpoints, using the imputation approach for change in body weight and change in KCCQ-CSS, respectively. Similar baseline variables were used as above with the baseline endpoint variable instead of baseline KCCQ-CSS.

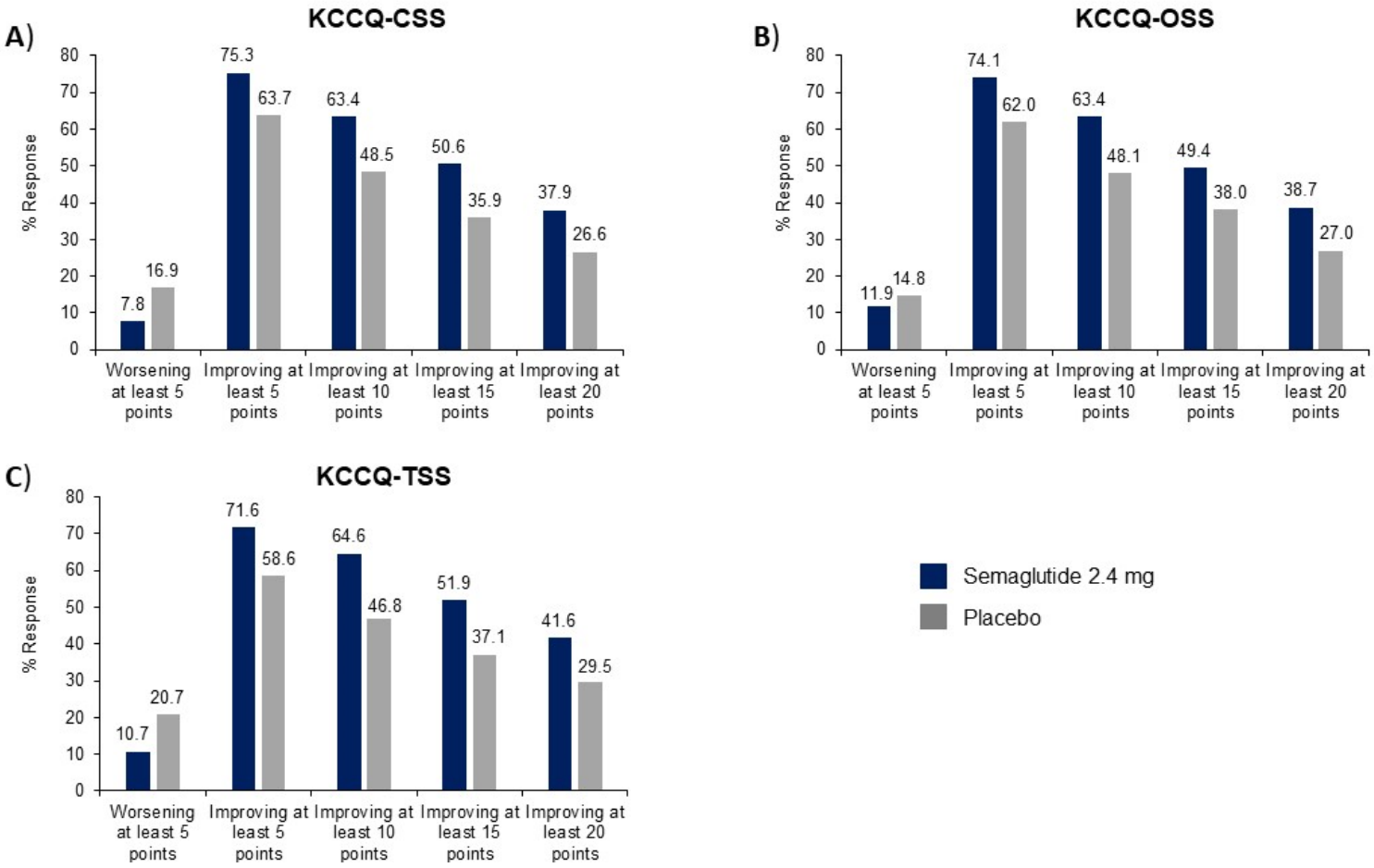
**Table S1. Change from baseline to Week 52 in KCCQ domains (in-trial data, MMRM model)**

| Domain | N | Change from baseline to Week 52 | ETD (95% CI) | *P*-value |
|---|---|---|---|---|
| **KCCQ-CSS** | | | | |
| Semaglutide 2.4 mg | 243 | 17.4 | 7.5 (4.7, 10.4) | <0.001 |
| Placebo | 237 | 9.8 | | |
| **KCCQ-OSS** | | | | |
| Semaglutide 2.4 mg | 243 | 17.4 | 7.1 (4.2, 10.0) | <0.001 |
| Placebo | 237 | 10.4 | | |
| **KCCQ-TSS** | | | | |
| Semaglutide 2.4 mg | 243 | 18.6 | 8.8 (5.7, 11.9) | <0.001 |
| Placebo | 237 | 9.8 | | |
| **KCCQ-PLS** | | | | |
| Semaglutide 2.4 mg | 243 | 16.5 | 6.6 (3.4, 9.8) | <0.001 |
| Placebo | 237 | 9.9 | | |
| **KCCQ-SLS** | | | | |
| Semaglutide 2.4 mg | 240 | 16.3 | 5.7 (1.9, 9.5) | 0.0034 |
| Placebo | 233 | 10.6 | | |
| **KCCQ-QoLS** | | | | |
| Semaglutide 2.4 mg | 243 | 19.0 | 7.9 (4.5, 11.4) | <0.001 |
| Placebo | 237 | 11.0 | | |
| **KCCQ-SBS** | | | | |
| Semaglutide 2.4 mg | 243 | 18.7 | 8.6 (5.3, 11.9) | <0.001 |
| Placebo | 237 | 10.1 | | |
| **KCCQ-SFS** | | | | |
| Semaglutide 2.4 mg | 243 | 18.6 | 9.3 (6.0, 12.5) | <0.001 |
| Placebo | 237 | 9.3 | | |

Data are from the in-trial period for the full analysis set using a mixed model for repeated measurements with randomised treatment and stratification (BMI<35.0 kg/$m^2$, BMI>=35.0 kg/$m^2$) as factors and relevant baseline KCCQ domain as covariate, all nested within visit during trial.

KCCQ indicates Kansas City Cardiomyopathy Questionnaire; CSS, Clinical Summary Score; OSS, Overall Summary Score; PLS, Physical Limitation Score; QoLS, Quality of Life Score; SBS, Symptom Burden Score; SFS, Symptom Frequency Score; SLS, Social Limitation Score; and TSS, Total Symptom Score.

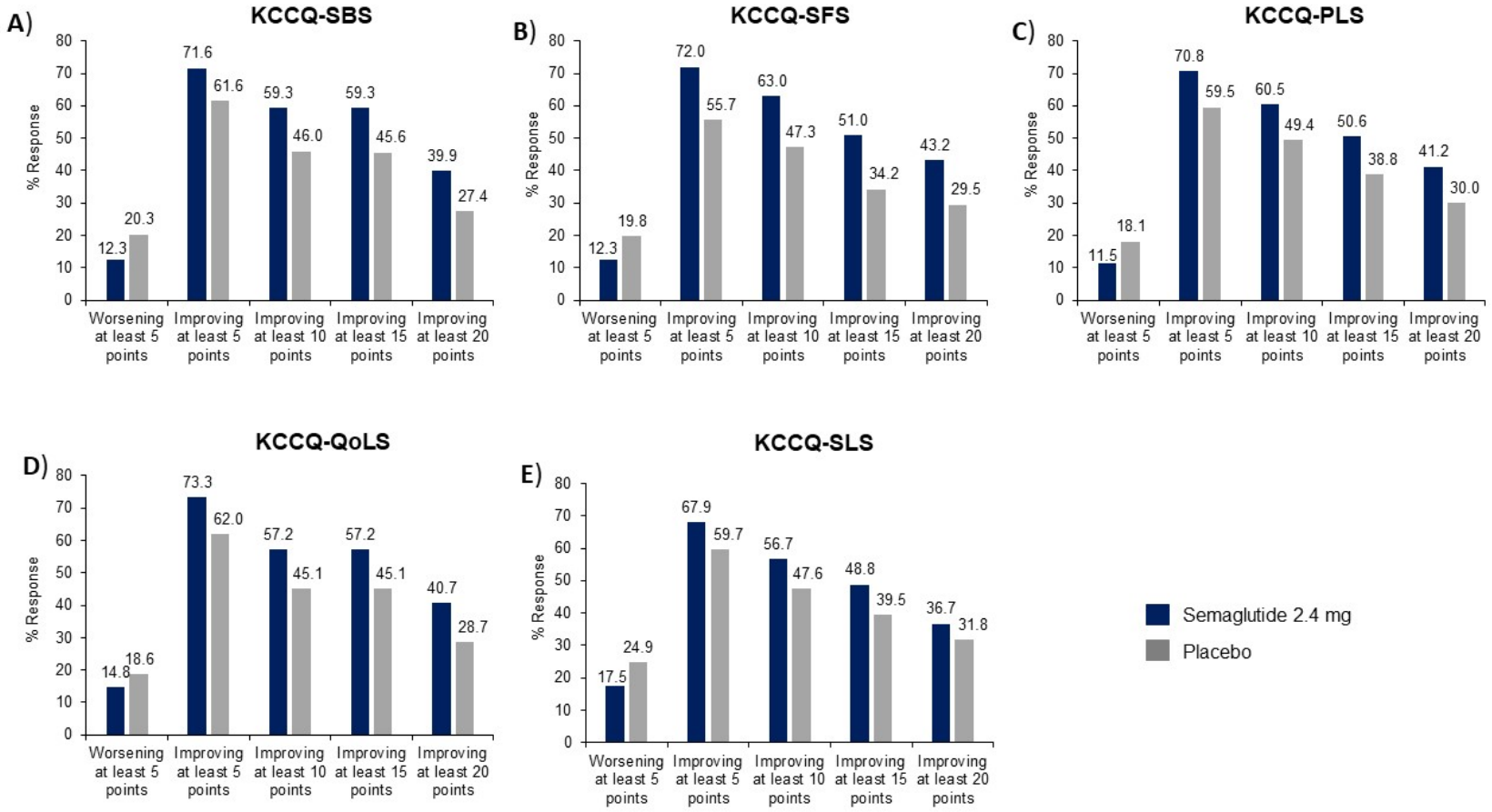
**Figure S1. Observed data for KCCQ subdomains A, CSS; B, OSS; and C, TSS responder analysis**




Data from in-trial period for the full analysis set. % Response reflects the observed data (participants with a KCCQ measurement at Week 52).

KCCQ indicates Kansas City Cardiomyopathy Questionnaire; CSS, Clinical Summary Score; OSS, Overall Summary Score; and TSS, Total Symptom Score.

**Figure S2. Observed data for KCCQ individual subdomains A, SBS; B, SFS; C, PLS; D, QoLS; and E, SLS responder analysis**

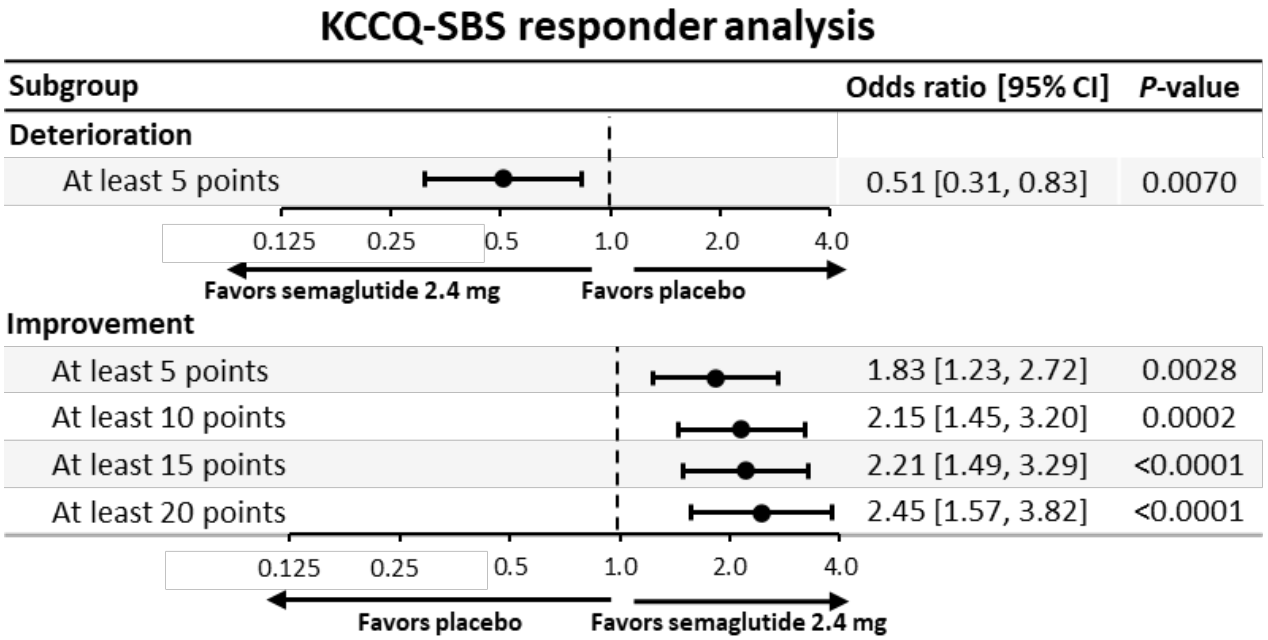



Data from in-trial period for the full analysis set. % Response reflects the observed data (participants with a KCCQ measurement at Week 52).

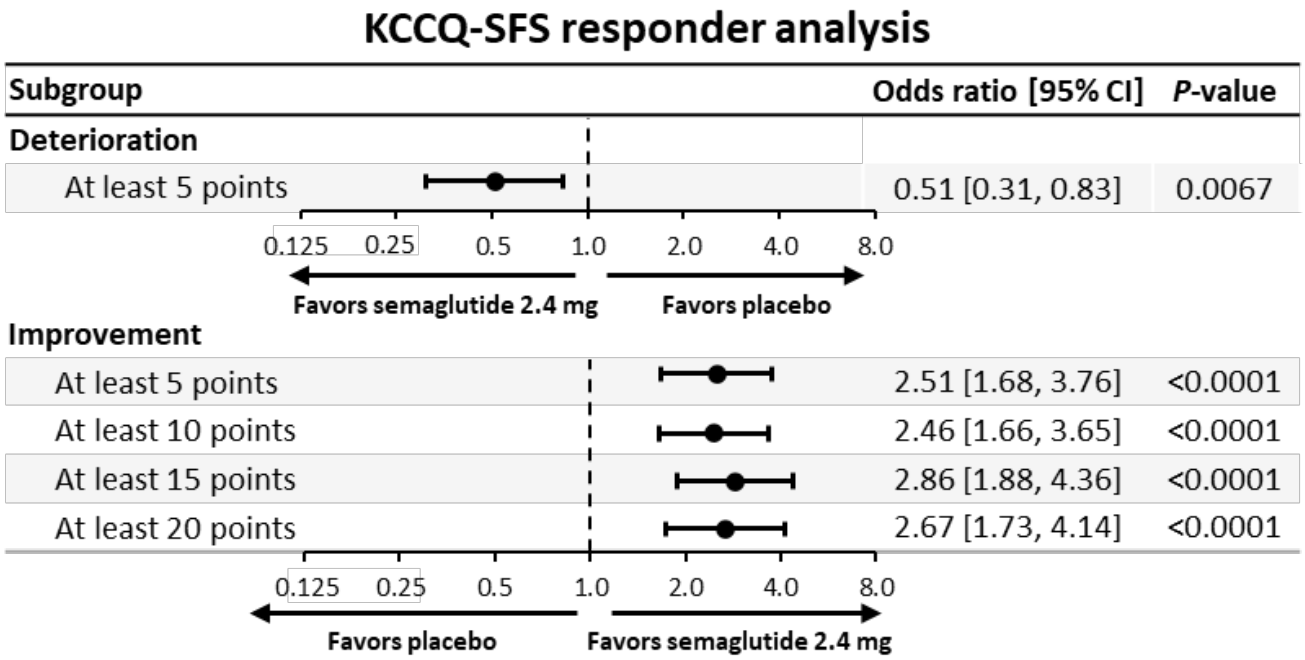
KCCQ indicates Kansas City Cardiomyopathy Questionnaire; PLS, Physical Limitation Score; QoLS, Quality of Life Score; SBS, Symptom Burden Score; SFS, Symptom Frequency Score; and SLS, Social Limitation Score.

**Figure S3. Responder analysis for A, KCCQ-SBS; B, KCCQ-SFS; C, KCCQ-PLS; D, KCCQ-QoLS; E, KCCQ-SLS.**

**A)**



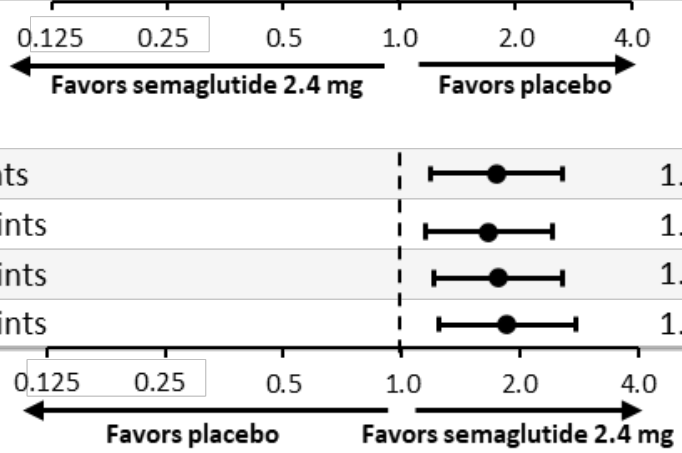
**B)**


KCCQ-SFS responder analysis
Subgroup
Odds ratio [95% CI]
P-value
Deterioration
At least 5 points
0.51 [0.31, 0.83]
0.0067
0.125
0.25
0.5
1.0
2.0
4.0
8.0
Favors semaglutide 2.4 mg
Favors placebo
Improvement
At least 5 points
2.51 [1.68, 3.76]
<0.0001
At least 10 points
2.46 [1.66, 3.65]
<0.0001
At least 15 points
2.86 [1.88, 4.36]
<0.0001
At least 20 points
2.67 [1.73, 4.14]
<0.0001
0.125
0.25
0.5
1.0
2.0
4.0
8.0
Favors placebo
Favors semaglutide 2.4 mg

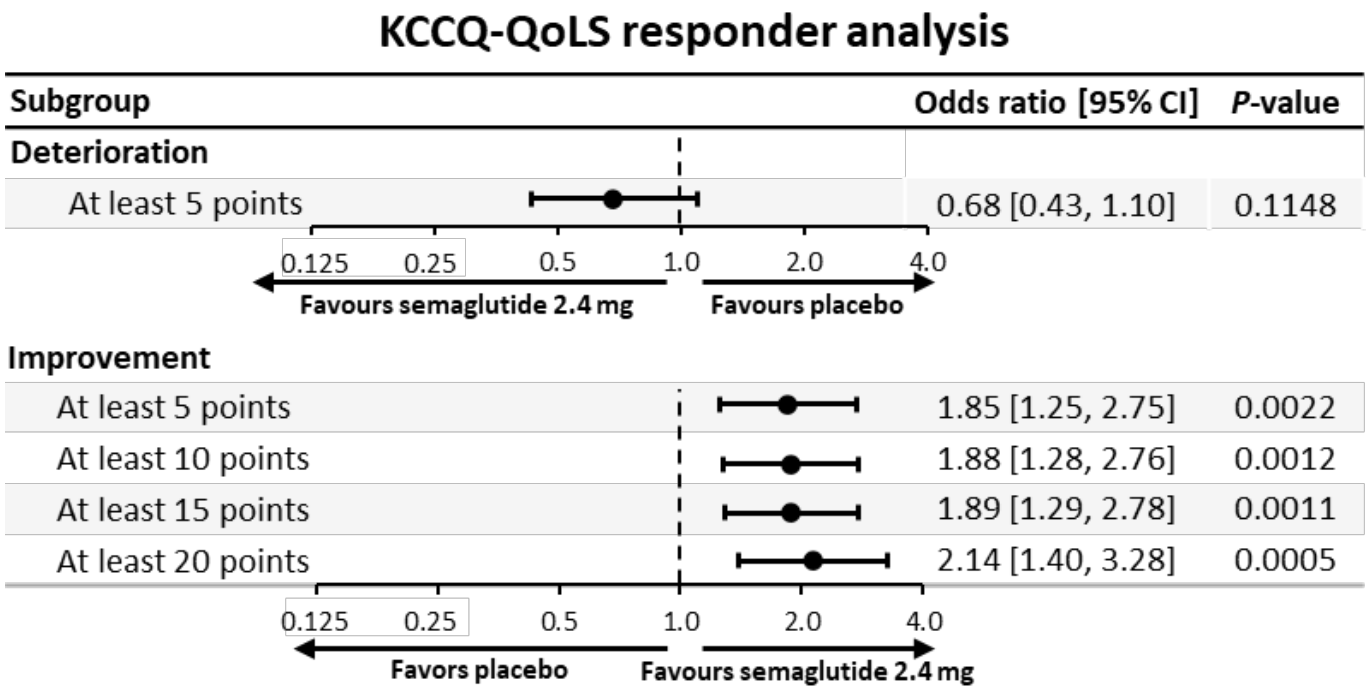
C)

## KCCQ-PLS responder analysis

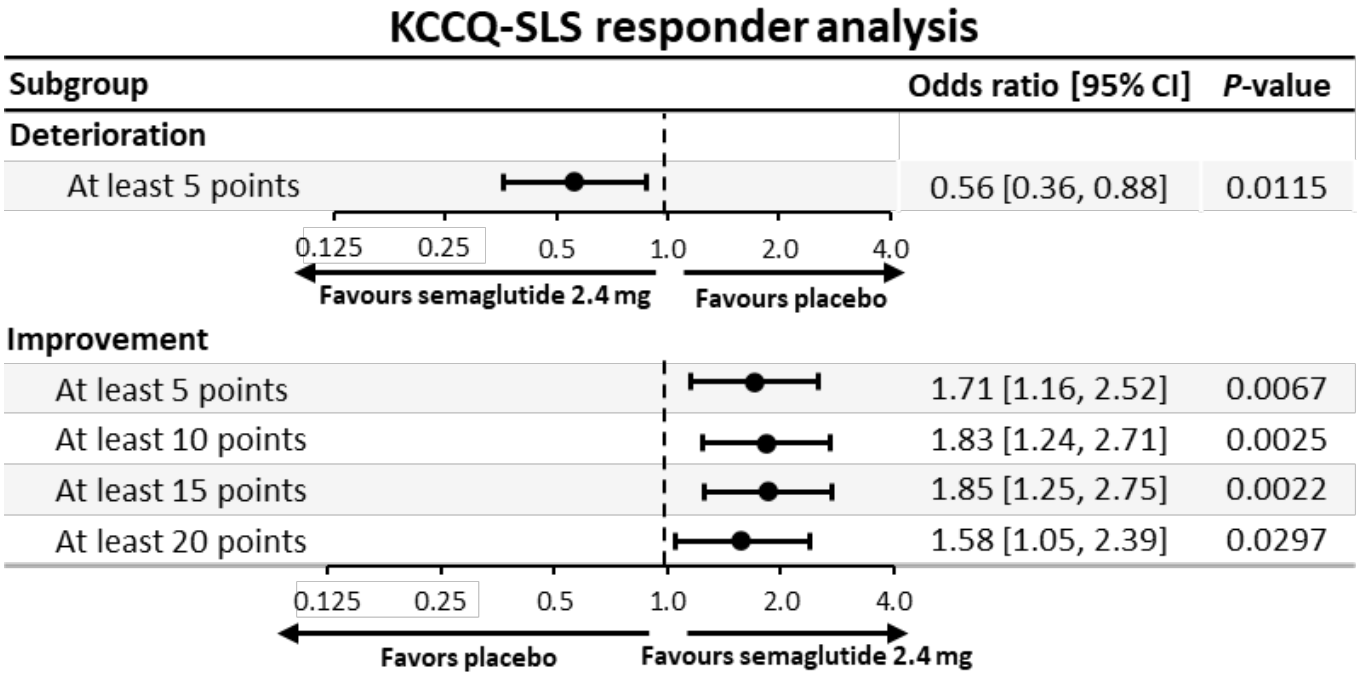
| Subgroup | Odds ratio [95% CI] | *P*-value |
|---|---|---|
| **Deterioration** | | |
| At least 5 points | 0.56 [0.34, 0.93] | 0.0255 |
| **Improvement** | | |
| At least 5 points | 1.74 [1.19, 2.56] | 0.0047 |
| At least 10 points | 1.66 [1.15, 2.41] | 0.0069 |
| At least 15 points | 1.76 [1.21, 2.57] | 0.0032 |
| At least 20 points | 1.85 [1.24, 2.77] | 0.0026 |



**D)**


KCCQ-QoLS responder analysis
Subgroup
Odds ratio [95% CI]
P-value
Deterioration
At least 5 points
0.68 [0.43, 1.10]
0.1148
0.125
0.25
0.5
1.0
2.0
4.0
Favours semaglutide 2.4 mg
Favours placebo
Improvement
At least 5 points
1.85 [1.25, 2.75]
0.0022
At least 10 points
1.88 [1.28, 2.76]
0.0012
At least 15 points
1.89 [1.29, 2.78]
0.0011
At least 20 points
2.14 [1.40, 3.28]
0.0005
0.125
0.25
0.5
1.0
2.0
4.0
Favors placebo
Favours semaglutide 2.4 mg

**E)**




Analysis of data from the in-trial period.
Week 52 responses were analyzed using a binary logistic regression model with randomized treatment and BMI group as factors and baseline KCCQ-CSS as covariate.
Missing observations due to other reasons than CV death or previous heart failure events (if non-retrieved) were multiple (x1000) imputed from retrieved participants of the same randomized treatment arm. Missing observations due to CV death or previous heart failure events were imputed using a composite strategy with the least favorable value determined during the trial.
BMI indicates body mass index, CI, confidence interval; CV, cardiovascular; KCCQ, Kansas City Cardiomyopathy Questionnaire; PLS, Physical Limitations Score; QoLS, Quality of Life Score; SBS, Symptom Burden Score; SFS, Symptom Frequency Score; and SLS, Social Limitations Score.