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# Tafamidis (transthyretin amyloid cardiomyopathy) –

## Addendum to Commission A20-102[1]

## Addendum

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**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| AE | adverse event |
| ATTR-CM | transthyretin amyloid cardiomyopathy |
| BSC | best supportive care |
| EAC | Endpoint Adjudication Committee |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| KCCQ | Kansas City Cardiomyopathy Questionnaire |
| MAR | missing at random |
| MI | multiple imputation |
| MMRM | mixed-effects model with repeated measures |
| NYHA | New York Heart Association |
| OSS | overall summary score |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SPC | Summary of Product Characteristics |
| TTR | Transthyretin |
| 6 MWT | 6-minute walking test |

# 1 Background

On 7 April 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-102 (Tafamidis – Benefit assessment according to §35a Social Code Book V) [1].

The ATTR-ACT study [2-4], which included patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM), was used in the dossier assessment. The ATTR-ACT study is a 3-arm, double-blind randomized controlled trial (RCT) comparing 2 different dosages of tafamidis meglumine (80 mg or 20 mg), each + best supportive care (BSC), against placebo + BSC. The arm with the 80 mg dosage of tafamidis meglumine was used for the dossier assessment (see dossier assessment A20-102 [1] for further details on the ATTR-ACT study).

In its comments [5], the pharmaceutical company (hereinafter referred to as "the company") submitted further analyses or additional information on the ATTR-ACT study [6] compared with the dossier.

The G-BA therefore commissioned IQWiG to assess the following analyses presented by the company in the dossier [6] or in the commenting procedure [5]:

- Assessment of the outcome "total hospitalization" from the dossier
- From the subsequently submitted data:
  - Subgroup analyses missing in the dossier for the operationalizations used in the dossier assessment; this affects the following outcomes: all-cause mortality, health-related quality of life, serious adverse events (SAEs), discontinuation due to adverse events (AEs)
  - Sensitivity analysis for the outcome "endurance" (6-minute walking test [6 MWT])
  - Assessment of the subsequently submitted information on the Endpoint Adjudication Committee (EAC) charter (with regard to cardiovascular hospitalization)
  - 15% threshold in health-related quality of life (Kansas City Cardiomyopathy Questionnaire [KCCQ] overall summary score [OSS])

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

## 2 Assessment

**Assessment of the outcome "total hospitalization" from the dossier**

In Module 4 B [6], the company presented results for the 2 outcomes "total hospitalization" and "cardiovascular hospitalization". The results of cardiovascular hospitalization were used for dossier assessment A20-102 [1]. The G-BA commissioned IQWiG to assess the outcome "total hospitalization".

The ATTR-ACT study recorded total hospitalization based on the frequency of hospitalizations from any cause. Results for the outcome "total hospitalization" are strongly dependent on the respective health care context, i.e. the possibilities and specifications for the different levels of care. In contrast to disease-specific hospitalization, as in the present case of hospitalization for cardiovascular causes, the severity of events recorded under the outcome "total hospitalization" is therefore potentially very heterogeneous. In contrast to the outcome "cardiovascular hospitalization", Module 4 B of the company did not describe the criteria for the relevance of the events leading to hospitalization for the outcome "total hospitalization". The outcome "total hospitalization" therefore appears less suitable for representing morbidity in the present case.

In accordance with the commission, the results on the outcome "total hospitalization" can be found in Appendix A. These are essentially congruent with the results for the outcome "cardiovascular hospitalization", including the effect modification for the overall rate for the characteristic of New York Heart Association (NYHA) classification.

**Assessment of the subsequently submitted information on the EAC charter (with regard to cardiovascular hospitalization)**

In the ATTR-ACT study, an independent EAC assessed whether a hospitalization was cardiovascular-related. An EAC charter defined which events were to be rated as cardiovascular. In dossier assessment A20-102, the risk of bias for the results of the outcome "cardiovascular hospitalization" was rated as high. The reason for this was the unclear influence of several version changes of the EAC charter on the results of this outcome.

With its comments [5], the company provided additional information on the version changes of the EAC charter.

The company described the changes of the individual versions in the comments. However, it did not present any data showing which specific events that occurred in the study were or were not recorded as cardiovascular hospitalizations due to these changes. The influence of the version changes on the results of the outcome "cardiovascular hospitalization" can therefore not be assessed. The information provided by the company on the version changes did not change the assessment of the risk of bias.

**Subgroup analyses for the outcome operationalizations used in the benefit assessment**

Results on subgroup analyses were available for the dossier assessment; however, not for the operationalizations used in the dossier assessment for the following outcomes: all-cause mortality, health-related quality of life, SAEs, and discontinuation due to AEs. Thus, considering the negative effect for the outcome "cardiovascular hospitalization" and because subgroup analyses for the characteristic of NYHA classification were not available for all outcomes, it could not be assessed whether there is any advantage at all or even lesser benefit for these outcomes in patients with NYHA class III cardiac failure.

With its comments [5], the company presented subgroup analyses for the outcomes "all-cause mortality", "health-related quality of life" (assessed using the KCCQ OSS), "SAEs", and "discontinuation due to AEs" for the following characteristics considered in benefit assessment A20-102: sex, NYHA classification and transthyretin (TTR) genotype.

There were no statistically significant effect modifications for the subgroup characteristics considered for the following outcomes: all-cause mortality, health-related quality of life (recorded using the KCCQ OSS), SAEs, and discontinuation due to AEs.

In comparison with dossier assessment A20-102, the subsequently submitted subgroup analyses therefore did not result in any further subgroup effects of tafamidis versus BSC for the outcomes mentioned.

**Sensitivity analysis for the outcome "endurance" (6 MWT)**

In dossier assessment A20-102, results from the mixed-effects model with repeated measures (MMRM) at month 30 were used for the outcome "endurance" (assessed using the 6 MWT). The risk of bias of these results was rated as high. This was due to a high proportion of patients with missing values or a large difference in missing values between the study arms (21% tafamidis + BSC versus 35% placebo + BSC).

Module 4 B of the company's dossier already provided 3 sensitivity analyses for the outcome "endurance" (assessed using the 6 MWT), but these were not sufficient for the benefit assessment:

- On the one hand, these are 2 pattern-mixture analyses that do not assume data not missing at random. In these analyses, the MMRM model used by the company adjusts for various assumed patterns by the occurrence of missing data. Thus, these analyses can in principle be regarded as suitable sensitivity analyses. However, in order to obtain the most unbiased results possible, this type of analysis requires an adequate recording of the true pattern of missing values. Since the actual mechanism for the occurrence of missing values is naturally unknown, however, the treatment effect cannot be reliably determined with these analyses either.
- On the other hand, this is the MMRM analysis at month 18, with the proportion of patients with missing values up to month 18 being lower than at month 30 (15%

tafamidis + BSC versus 25% placebo + BSC). This analysis at month 18 provides a potentially unbiased estimation of the treatment effect due to the higher response rates, but unlike the results at month 30, does not cover the entire course of the study.

With its comments [5], the company presented one further sensitivity analysis for this outcome, in which missing values up to month 30 were imputed using multiple imputation (MI). This analysis provides potentially unbiased estimations if the missing at random (MAR) assumption holds. However, because of the strong decrease in response rates up to month 30, which differed differentially between the treatment groups, the random missing of the values is questionable. Thus, the results of this analysis for the 30-month period have a high risk of bias. Furthermore, the methods were not sufficiently described in the comments, e.g. there was no information on which variables were used for the MI.

The results of the sensitivity analyses for the outcome "endurance" (recorded using the 6 MWT; given in metres) are listed below (mean difference [95% confidence interval]; p-value):

- pattern mixture model 1: 61.31 [36.00; 86.62]; < 0.001
- pattern mixture model 2: 63.36 [29.25; 97.47]; < 0.001
- MMRM analysis at month 18: 45.04 [27.30; 62.79]; < 0.001
- missing values up to month 30 imputed by MI: 70.84 [48.01; 93.66]; < 0.001

The sensitivity analysis presented by the company in the comments did not change the assessment regarding the high risk of bias for the results of the outcome "endurance". However, all sensitivity analyses presented also showed a statistically significant difference in favour of tafamidis for the outcome "endurance". The result of the primary analysis was thus robust in terms of statistical significance. Furthermore, the estimated effects in all sensitivity analyses as well as in the primary analysis were so large that in the overall view of the analyses presented, the certainty of results for the outcome "endurance" was not reduced, despite a high risk of bias of the results.

**15% threshold in health-related quality of life (KCCQ OSS)**

The responder analyses on health-related quality of life (recorded using the KCCQ OSS, including time to deterioration by ≥ 5 points) presented by the company in Module 4 B of the dossier were not used for benefit assessment A20-102 with reference to IQWiG's *General Methods* 6.0 [7]. According to these methods, for a response criterion to reflect with sufficient certainty a patient-noticeable change, it has to correspond to at least 15% of the scale range of an instrument if prespecified (exactly 15% of the scale range in post-hoc analyses).

Subsequent to the hearing, the company submitted a responder analysis with a response threshold of 15% of the scale range for the outcome mentioned above. This corresponds to a response threshold of 15 points for the analyses of the KCCQ OSS results. Therefore, the analysis for the time to deterioration by ≥ 15 points was used for the present assessment.

***Risk of bias***

For the risk of bias of the results for the outcome of health-related quality of life (recorded using the KCCQ OSS), the information provided by the company in the commenting procedure overall did not result in a deviating assessment of the risk of bias in comparison with benefit assessment A20-102 [1]. Thus, there is still a low risk of bias of the results.

***Results of the analyses with a response threshold of 15% of the scale range***

The results of the responder analysis with a response threshold of 15% of the scale range for the outcome of health-related quality of life (recorded using the KCCQ OSS) are presented in Table 1.

Table 1: Results (health-related quality of life, time to event) – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

| Study<br>Outcome category<br>Outcome | Tafamidis + BSC | | Placebo + BSC | | Tafamidis + BSC vs. placebo + BSC |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value[a] |
| **ATTR-ACT** | | | | | |
| **Health-related quality of life** | | | | | |
| Health-related quality of life (KCCQ OSS) | 176 | 30.46 [30.03; NC] | 177 | 18.30 [17.71; 23.95] | 0.49 [0.35; 0.67]; < 0.001 |
| Deterioration by ≥ 15 points | | 64 (36.4) | | 95 (53.7) | |

a. HR, CI and p-value: Cox proportional hazards model adjusted for baseline value and TTR genotype.

BSC: best supportive care; CI: confidence interval; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; OSS: overall summary score; RCT: randomized controlled trial; TTR: transthyretin; vs.: versus

A statistically significant difference in favour of tafamidis + BSC in comparison with placebo + BSC was shown for the outcome "health-related quality of life" recorded with the KCCQ OSS. This resulted in a hint of an added benefit of tafamidis + BSC in comparison with BSC for this outcome.

## 2.1 Probability and extent of added benefit

Taking into account dossier assessment A20-102, probability and extent of the added benefit at outcome level are derived in Table 2. Based on the results presented in Chapter 2 and on the results described in the dossier assessment [1], the extent of the added benefit is assessed at outcome level.

Irrespective of the assessment of the subsequently submitted data on the risk of bias in the outcomes "cardiovascular hospitalization" and "endurance" (recorded using the 6 MWT), the certainty of conclusions is reduced due to the formulation in the ATTR-ACT study, which deviated from the Summary of Product Characteristics (SPC) [8] (see dossier assessment A20-102 for details). Thus, at most hints, e.g. of an added benefit, can be determined for all outcomes.

Table 2: Extent of added benefit at outcome level: tafamidis + BSC vs. placebo + BSC (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Tafamidis + BSC vs. placebo + BSC**<br>**Median time to event (months) or annual rate or mean change at month 30 or proportion of events (%)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Mortality** | | |
| All-cause mortality | Median: NA vs. NA<br>HR: 0.65 [0.45; 0.93];<br>p = 0.020<br>probability: "hint" | Outcome category: mortality<br>$0.85 \leq CI_u < 0.95$<br>added benefit, extent: "considerable" |
| **Morbidity** | | |
| Cardiovascular hospitalization | | |
| NYHA class I or II | Annual rate: 0.35 vs. 0.71<br>rate ratio: 0.49 [0.38; 0.64];<br>p < 0.001<br>proportions of events: 43.8% vs. 61.4%<br>RR: 0.71 [0.56; 0.91]<br>p = 0.007<br>probability: "hint" | Outcome category: serious/severe symptoms/late complications<br>rate ratio: $CI_u < 0.75$, risk ≥ 5%<br>RR: $0.90 \leq CI_u < 1.00$<br>added benefit, extent: "considerable"[c] |
| NYHA class III | Annual rate: 0.99 vs. 0.68<br>rate ratio: 1.46 [1.07; 2.00];<br>rate ratio: 0.68 [0.50; 0.93][d]<br>p = 0.018<br>proportions of events: 78.2% vs. 58.7%<br>RR: 1.33 [1.04; 1.71]<br>RR: 0.75 [0.58; 0.96][d]<br>probability: "hint" | Outcome category: serious/severe symptoms/late complications<br>rate ratio: $0.90 \leq CI_u < 1.00$<br>RR: $0.90 \leq CI_u < 1.00$<br>Lesser benefit, extent: "minor"[e] |
| Endurance (6 MWT) | Mean change: −54.77 vs. −130.54<br>MD: 75.77 [55.99; 95.55];<br>p < 0.001<br>probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>added benefit, extent: "non-quantifiable" |
| Health status (EQ-5D VAS) | Mean change: −3.43 vs. −12.92<br>MD: 9.49 [6.05; 12.94];<br>p < 0.001<br>Hedges' g: 0.60 [0.38; 0.83][f]<br>probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>added benefit, extent: "non-quantifiable" |

Table 2: Extent of added benefit at outcome level: tafamidis + BSC vs. placebo + BSC (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Tafamidis + BSC vs. placebo + BSC**<br>**Median time to event (months) or annual rate or mean change at month 30 or proportion of events (%)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Health-related quality of life** | | |
| Health-related quality of life (KCCQ OSS) | Median: 30.46 vs. 18.30 months<br>HR: 0.49 [0.35; 0.67];<br>p < 0.001<br>probability: "hint" | Outcome category: health-related quality of life<br>$CI_u$ < 0.75, risk ≥ 5%<br>added benefit, extent: "major" |
| **Side effects** | | |
| SAEs | Proportions of events: 60.2% vs. 57.6%<br>RR: 1.05 [0.88; 1.24];<br>p = 0.683 | Greater/lesser harm not proven |
| Discontinuation due to AEs | Proportions of events: 11.4% vs. 15.8%<br>RR: 0.72 [0.42; 1.23];<br>p = 0.247 | Greater/lesser harm not proven |
| Dyspnoea (PT, AE)<br>NYHA classification | | |
| NYHA class I or II | Proportions of events: 14.0% vs. 35.1%<br>RR: 0.39 [0.24; 0.65];<br>p < 0.001<br>probability: "hint" | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>lesser harm, extent: "considerable" |
| NYHA class III | Proportions of events: 21.8% vs. 23.8%<br>RR: 0.94 [0.49; 1.83];<br>p = 0.865 | Outcome category: non-serious/non-severe side effects<br>greater/lesser harm not proven |

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval ($CI_u$).
c. The assessment of the extent as "considerable" results from the joint consideration of the results on the rate ratio (extent "major") and the proportion of patients with event (extent "minor").
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. The assessment of the extent as "minor" results from the joint consideration of the results on the rate ratio (extent "minor") and the proportion of patients with event (extent "minor").
f. If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be inferred.

AE: adverse event; BSC: best supportive care; CI: confidence interval; $CI_u$: upper limit of confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; MD: mean difference; NYHA: New York Heart Association; OSS: overall summary score; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; TTR: transthyretin; VAS: visual analogue scale; vs.: versus; 6 MWT: 6-minute walking test

## 2.2 Overall conclusion on added benefit

Table 3 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 3: Positive and negative effects from the assessment of tafamidis in comparison with BSC

| **Positive effects**[a] | **Negative effects** |
|---|---|
| Mortality<br>▪ All-cause mortality: hint of an added benefit – extent "considerable" | – |
| Serious/severe symptoms/late complications<br>▪ Cardiovascular hospitalization:<br>▫ NYHA class I + II: hint of an added benefit – extent: "considerable" | Serious/severe symptoms/late complications<br>▪ Cardiovascular hospitalization:<br>▫ NYHA class III: hint of lesser benefit – extent: "minor" |
| Non-serious/non-severe symptoms/late complications<br>▪ Endurance (6 MWT): hint of an added benefit – extent: "non-quantifiable"<br>▪ Health status: hint of an added benefit – extent: "non-quantifiable" | – |
| Health-related quality of life<br>▪ Health-related quality of life (KCCQ OSS): hint of an added benefit – **extent "major"** | – |
| Non-serious/non-severe side effects:<br>▪ Dyspnoea (PT, AE)<br>▫ NYHA class I + II: hint of an added benefit – extent: "considerable" | – |
| a. Changes in comparison with dossier assessment A20-102 are printed in **bold**.<br>AE: adverse event; BSC: best supportive care; KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; OSS overall summary score; PT: Preferred Term; 6 MWT: 6-minute walking test | |

Taking into account the data subsequently submitted in the commenting procedure, there are changes compared with dossier assessment A20-102.

The subsequently submitted subgroup analyses for the outcomes "all-cause mortality", "health-related quality of life", "SAEs" and "discontinuation due to AEs" showed no further statistically significant effect modifications. Thus, the positive and negative effects are still assessed separately for patients with NYHA class I + II cardiac failure and for patients with NYHA class III cardiac failure.

**Patients with NYHA class I + II cardiac failure at baseline**

There were only positive effects for patients with NYHA class I + II cardiac failure at baseline. The effect in the outcome "health-related quality of life" (assessed using KCCQ OSS) is decisive for the conclusion on the added benefit. For this outcome, for which the positive effect was not quantifiable in the dossier assessment, there is now an added benefit of tafamidis +

BSC compared with BSC of major extent. The other positive effects in the outcomes "all-cause mortality", "cardiovascular hospitalization", "endurance", "health status" and "dyspnoea" (in some cases with considerable extent) remain unchanged compared with the dossier assessment.

In summary, there is a hint of major added benefit of tafamidis + BSC in comparison with BSC for patients with ATTR-CM and with NYHA class I + II cardiac failure at baseline.

**Patients with NYHA class III cardiac failure at baseline**

There were mainly positive effects and one negative effect for patients with NYHA class III cardiac failure at baseline. For the outcome "health-related quality of life", for which the positive effect was not quantifiable in the dossier assessment, there is now an added benefit of tafamidis + BSC compared with BSC of major extent. The other positive effects in the outcomes "all-cause mortality", "endurance" and "health status" (in some cases with considerable extent) remain unchanged compared with the dossier assessment. These were accompanied by lesser benefit of minor extent in the outcome "cardiovascular hospitalization".

In summary, there is a hint of considerable added benefit of tafamidis + BSC in comparison with BSC for patients with ATTR-CM and with NYHA class I + III cardiac failure at baseline.

## 2.3 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of tafamidis from dossier assessment A20-102.

The following Table 4 shows the result of the benefit assessment of tafamidis under consideration of dossier assessment A20-102 and the present addendum.

Table 4: Tafamidis – probability and extent of added benefit

| **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit[b]** |
|---|---|---|
| Wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) in adult patients | Best supportive care[c, d, e] | ▪ Patients with NYHA class I + II cardiac failure: hint of **major added benefit**<br>▪ Patients with NYHA class III cardiac failure: hint of **considerable added benefit** |

a. Presentation of the ACT specified by the G-BA.
b. Changes in comparison with dossier assessment A20-102 are printed in **bold**.
c. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
d. It is assumed that a patient-specific adequate treatment of the respective organ manifestation corresponding to the state of medical knowledge is carried out in the study arms, taking into account the special features of the disease hATTR amyloidosis, and is documented as concomitant treatment.
e. It is assumed that liver transplantation is not an option at the time of therapy with tafamidis.

ACT: appropriate comparator therapy; ATTR-CM: transthyretin amyloid cardiomyopathy; G-BA: Federal Joint Committee; hATTR: hereditary transthyretin amyloidosis; NYHA: New York Heart Association

The G-BA decides on the added benefit.

## 3 References

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## Appendix A – Supplementary presentation of the outcome "total hospitalization"

Table 5: Results (morbidity, dichotomous) – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

| Study<br>Outcome category | Tafamidis + BSC | | Placebo + BSC | | Tafamidis + BSC vs. placebo + BSC |
|---|---|---|---|---|---|
| **Outcome** | **N** | **Rate [95% CI][a]** | **N** | **Rate [95% CI][a]** | **Rate ratio [95% CI]; p-value[a]** |
| **ATTR-ACT** | | | | | |
| **Morbidity** | | | | | |
| **Total hospitalization** | | | | | |
| Rate | 176 | 0.96 [0.86; 1.06] | 177 | 1.16 [1.05; 1.29] | 0.82 [0.71; 0.95]; 0.009 |
| | | **Patients with event n (%)** | | **Patients with event n (%)** | **RR [95% CI]; p-value[b]** |
| Patients with event | 176 | 125 (71.0) | 177 | 136 (76.8) | 0.92 [0.82; 1.05]; 0.247 |

a. Mean rates with CI (per treatment group) as well as rate ratio with CI and p-value (group comparison): Poisson regression with the variables treatment, TTR genotype, NYHA classification and the interaction terms between treatment and TTR genotype as well as between treatment and NYHA classification; according to the company, adjusted for the observation period with treatment. It remains unclear whether this is the observation or treatment period.
b. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [9]).

BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least one) event; N: number of analysed patients; NYHA: New York Heart Association; RCT: randomized controlled trial; RR: relative risk; TTR: transthyretin; vs.: versus

Table 6: Subgroups (morbidity, dichotomous) – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

| Study<br>Outcome | Tafamidis + BSC | | Placebo + BSC | | Tafamidis + BSC vs. placebo + BSC | |
|---|---|---|---|---|---|---|
| Characteristic<br>Subgroup | N | Rate<br>[95% CI][a] | N | Rate<br>[95% CI][a] | Rate ratio<br>[95% CI][a] | p-value[a] |
| **ATTR-ACT** | | | | | | |
| **Total hospitalization** | | | | | | |
| NYHA classification | | | | | | |
| NYHA class I or II | 121 | 0.76<br>[0.66; 0.87] | 114 | 1.14<br>[1.01; 1.28] | 0.67 [0.56; 0.80] | < 0.001 |
| NYHA class III | 55 | 1.52<br>[1.29; 1.79] | 63 | 1.21<br>[1.01; 1.44] | 1.26 [0.99; 1.61] | 0.061 |
| Total | | | | | Interaction: | < 0.001[b] |

a. Mean rates with CI (per treatment group) as well as rate ratio with CI and p-value (group comparison): Poisson regression with the variables treatment, TTR genotype, NYHA classification and the interaction terms between treatment and TTR genotype as well as between treatment and NYHA classification; according to the company, adjusted for the observation period with treatment. It remains unclear whether this is the observation or treatment period.
b. Poisson regression with corresponding interaction term.

BSC: best supportive care; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; NYHA: New York Heart Association; RCT: randomized controlled trial; TTR: transthyretin; vs.: versus