Sacubitril/valsartan (heart failure, children and adolescents)

Addendum to Project A23-56 (dossier assessment)[1]

ADDENDUM

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[1] Translation of addendum *Sacubitril/Valsartan (Herzinsuffizienz, Kinder und Jugendliche) – Addendum zum Projekt A23-56 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 24 October 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-56 (Sacubitril/valsartan – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the analyses subsequently submitted by the pharmaceutical company (hereinafter referred to as "the company") in the commenting procedure [2], taking into account the information provided in the dossier [3]:

- subsequently submitted analyses of the side effects in which the disease-specific Preferred Terms (PTs) were excluded
- data on observation periods after study discontinuation and treatment discontinuation

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

The research question in Project A23-56 (sacubitril/valsartan) [1] was to assess the added benefit of sacubitril/valsartan in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in children and adolescents aged 1 year or older with symptomatic chronic heart failure with left ventricular systolic dysfunction.

The check for completeness of the study pool identified no relevant study for the direct comparison of sacubitril/valsartan versus the ACT BSC. In its dossier [3], the company deviated from the G-BA's definition of the ACT, used treatment of physician's choice with enalapril as the ACT, and, based on this comparator therapy, included the randomized controlled trial (RCT) PANORAMA-HF on the comparison of sacubitril/valsartan with enalapril in its study pool.

The RCT PANORAMA-HF was not used for the benefit assessment of sacubitril/valsartan, as it did not investigate the comparison with the G-BA's ACT. Irrespective of the research question described above, the G-BA had commissioned IQWiG to conduct an analysis (methodological review and presentation of results) of the data of the PANORAMA-HF study presented in the company's dossier [3].

With its comments [2], the company subsequently submitted further data of the PANORAMA-HF study. These data include analyses of the outcomes of serious adverse events (SAEs) and discontinuation due to adverse events (AEs), in each of which disease-specific events were excluded. In addition, the company submitted analyses of observation periods after study and treatment discontinuation.

These subsequently submitted analyses are considered usable.

2.1 Subsequently submitted analyses of side effects

In the dossier [3], the analysis of SAEs and discontinuations due to AEs included not only treatment-related events but also a large number of events that can be attributed to the symptoms of the underlying disease (e.g. heart failure). To allow an adequate assessment of side effects, the overall rates of SAEs and discontinuations due to AEs would have to be analysed also without disease-related events. The overall rates available in the dossier for the outcomes of SAEs and discontinuations due to AEs were therefore not usable to assess the study [1].

Based on the occurred events, the company excluded the PTs cardiac failure, cardiac failure acute, cardiac failure congestive, and ventricular dysfunction for the overall rates of SAEs and discontinuations due to AEs in the analyses subsequently submitted. This analysis is comprehensible and appropriate. The analyses of SAEs and discontinuations due to AEs subsequently submitted by the company are presented in Table 1.

Table 1: Results (side effects, dichotomous) – RCT, direct comparison: sacubitril/valsartan vs. enalapril

Study Outcome category Outcome	Sacubitril/valsartan		Enalapril		Sacubitril/valsartan vs. enalapril
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
PANORAMA-HF					
Side effects					
SAEs[b]	182	57 (31.3)	184	53 (28.8)	1.09 [0.80; 1.49]; 0.683
Discontinuation due to AEs[b]	182	10 (5.5)	184	11 (6.0)	0.92 [0.40; 2.11]; 0.892

a. Unconditional exact test (CSZ method according to [4]).
b. Excluding the disease-specific PTs cardiac failure, cardiac failure acute, cardiac failure congestive, and ventricular dysfunction.

AE: adverse event; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

No statistically significant difference was found between treatment groups for either of the overall rates of the outcomes of SAEs or discontinuation due to AEs.

2.2 Data subsequently submitted on observation periods

It was unclear in the assessment of the PANORAMA-HF study [1] whether the outcome of severe cardiac failure events was still recorded in all operationalizations even after treatment discontinuation. Due to this uncertainty and the high proportion of patients who discontinued treatment (20% versus 25%), the risk of bias for the results of the outcome of severe cardiac failure events was rated as high.

In addition, due to the consideration of 52 treatment weeks in the PANORAMA-HF study, there were individual observation periods, which were not presented in the company's dossier, however. Thus, besides the aspects mentioned above, there was an increased risk of bias for the results of all outcomes.

The company explained in its comments that AEs continued to be recorded as part of the planned visit schedule even after discontinuation of the study therapy. Thus, according to the company, it was not the rates of patients who discontinued study therapy prematurely that were relevant for assessing the risk of bias of the side effects outcomes and the outcome of severe cardiac failure events, but rather the rates of patients who completely discontinued study participation prematurely (8.8% sacubitril/valsartan versus 13.0% enalapril). In addition, the company stated in the oral hearing that the severe cardiac failure events were also recorded until the end of the study [5].

Furthermore, the company submitted data on observation periods as part of the comments (see Table 2).

Table 2: Information on the course of the study – RCT, direct comparison: valsartan vs. enalapril

Study **Duration of the study phase**	**Sacubitril/valsartan** **N = 182**	**Enalapril** **N = 185**
PANORAMA-HF		
Observation period [days]		
Mean (SD)	365 (61)	349 (87)
N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation		

Taking into account the information from the commenting procedure and the subsequently submitted data on the observation periods, the risk of bias for the outcomes of severe cardiac failure events, SAEs, discontinuation due to AEs, angioedema, hyperkalaemia, hypertension, and nervous system disorders is assessed as low (see Table 3).

Table 3: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: sacubitril/valsartan vs. enalapril

Study		**Outcomes**									
	Study level	**All-cause mortality**[a]	**Severe cardiac failure events**[b]	**Symptoms (PGIS, PGIC)**	**Health-related quality of life (PedsQL)**	**SAEs**	**Discontinuation due to AEs**	**Angioedema (PT, AEs)**	**Hyperkalaemia (PT, SAEs)**	**Hypotension (PT, SAEs)**	**Nervous system disorders (SOC, SAEs)**
PANORAMA-HF	L	L	L	H[c]	H[c]	L	L	L	L	L	L

a. Deaths were recorded as AEs.

b. For the outcome of severe cardiac failure events, analyses of the following operationalizations are used:
- UNOS status 1A for heart transplant or equivalent
- VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support
- hospitalization for cardiac failure

c. Overall high proportion (PGIS/PGIC: approx. 25%, PedsQL: approx. 30%) of patients who were not included in the analyses or for whom the worst possible event was assumed.

AE: adverse event; ECMO: extracorporeal membrane oxygenation; H: high; L: low; PedsQL: Pediatric Quality of Life Inventory; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; UNOS: United Network of Organ Sharing; VAD: ventricular assist device

2.3 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion on the added benefit of sacubitril/valsartan drawn in dossier assessment A23-56 [1].

The following Table 4 shows the result of the benefit assessment of sacubitril/valsartan under consideration of dossier assessment A23-56 and the present addendum.

Table 4: Sacubitril/valsartan – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Children and adolescents aged 1 year or older with symptomatic chronic heart failure with left ventricular systolic dysfunction	BSC[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC 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. In accordance with notes by the G-BA, infants, children and adolescents in both study arms are assumed to receive optimal care. Patients with concomitant symptoms of the underlying disease(s) or risk factors, such as tachycardia, tachypnoea, oedema, ascites, pain, hypertension, or cardiac arrhythmias, must receive individual treatment in accordance with the generally recognized state of scientific knowledge. It should be possible to adapt the basic/concomitant medication to the patients' individual needs in both study arms. In this context, treatment adjustment can comprise both dose adjustments and treatment switches/initiations to respond to newly developed symptoms or the deterioration of existing symptoms.
c. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; G-BA: Federal Joint Committee; SGB: Social Code Book

The G-BA decides on the added benefit.

3 References

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