Vutrisiran
(hereditary transthyretin amyloidosis with polyneuropathy 1)

Addendum to Project A22-114
(dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
FAP	Familial Amyloidotic Polyneuropathy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
hATTR amyloidosis	hereditary transthyretin amyloidosis
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mNIS+7	modified Neuropathy Impairement Score +7
NCI	National Cancer Institute
NIS	Neuropathy Impairment Score
Norfolk QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy
PND	Polyneuropathy Disability
PT	Preferred Term
RCT	randomized controlled trial
R-ODS	Rasch-Built Overall Disability Score
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

1 Background

On 21 February 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A22-114 (Vutrisiran– Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the analyses on side effects from the HELIOS-A study subsequently submitted by the pharmaceutical company (hereinafter referred to as "the company") in the commenting procedure. The outcomes of modified Neuropathy Impairment Score +7 (mNIS+7), Neuropathy Impairment Score (NIS), Familial Amyloidotic Polyneuropathy (FAP) stage, Polyneuropathy Disability (PND) score and Rasch-Built Overall Disability Score (R-ODS) from the HELIOS-A study will also be assessed.

The assessment was conducted under consideration of the information provided in the dossier.

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

In benefit assessment A22-114, the randomized controlled trial (RCT) HELIOS-A was used to assess the added benefit of vutrisiran compared to the appropriate comparator therapy (ACT) in patients with hereditary transthyretin amyloidosis (hATTR amyloidosis) with stage 1 or 2 polyneuropathy.

2.1 Assessment of the outcomes on side effects in the HELIOS-A study

In the HELIOS-A study, the (ACT was implemented with the drug patisiran. Patisiran is administered intravenously and infusion related reactions are a known side effect. However, as vutrisiran is administered subcutaneously, the event "infusion related reaction" could only be recorded in the comparator arm. With its comment, the company presented analyses in which it included the adverse events (AEs) that had been hidden behind the preferred term (PT) "infusion related reaction" in the previously submitted analyses. It presents the resulting number of patients with event for both study arms at the level of the System Organ Class (SOC) or PTs. No PT was assigned to the category of severe AEs or discontinuation due to AEs. The tables on common AEs and common serious AEs (SAEs) were adjusted due to this analysis (see Appendix D of the full dossier assessment). The changes are printed in **bold**. Moreover, this yielded further specific AEs in the category of SAEs (see Section 2.1.2).

New analyses on the overall rates of AEs and SAEs are not available. As already described in the dossier assessment, no changes in the number of patients with event were to be expected for these superordinate AE outcomes as a result of the new analysis. It is therefore assumed that the number of patients with event remained unchanged in the overall rates of AEs and SAEs.

2.1.1 Infusion-related reaction

In the HELIOS-A study, no specific AEs were predefined that could represent infusion-related reactions and at the same time could be recorded in both study arms. Therefore, there are no usable data for this outcome even after the comments. However, based on the analyses submitted with the company’s comments, the events underlying the outcome have now been recorded via the specific AEs.

2.1.2 Further specific AEs

The analyses on AEs submitted with the company's comments lead to the fact that, in addition to the outcomes already assessed in the dossier assessment, the following specific AEs are included in the benefit assessment as patient-relevant outcomes:

- Gastrointestinal disorders (SOC, SAE)
- General disorders and administration site conditions (SOC, SAE)

Table 1 shows the results of the two specific AEs “gastrointestinal disorders” (SAE) and “general disorders and administration site conditions” (SAE), which were newly added due to the data submitted with the company’s comment.

Table 1: Results (side effects, new specific AEs) – RCT, direct comparison: vutrisiran versus patisiran

Study outcome category outcome	Vutrisiran		Patisiran		Vutrisiran vs. patisiran
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
HELIOS-A					
Side effects[b]					
Gastrointestinal disorders (SOC, AEs)[c]	122	1 (0.8)	42	3 (7.1)	0.11 [0.01; 1.07][d] 0.031
General disorders and administration site conditions (SOC, SAE)[e]	122	1 (0.8)	42	4 (9.5)	0.09 [0.01; 0.749][d] 0.008

a. p-value: IQWiG calculation (unconditional exact test, CSZ method according to [2]).
b. During the 18-month randomized treatment phase of vutrisiran vs. patisiran (until week 84); including a relevant proportion of events that can be both side effects and symptoms.
c. Included PTs are “constipation” and “lip oedema”.
d. Effect and CI: Institute's calculation.
e. Included PTs are “asthenia”, “general physical health deterioration”, “phlebitis at the infusion site”, “chest pain”, “heat sensation” and “swelling face”.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; SOC: System Organ Class: RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

For each of the two added specific AEs “gastrointestinal disorders” (SAE) and “general disorders and administration site conditions” (SAE), there was a statistically significant difference between the treatment groups in favour of vutrisiran. In each case, there was a hint of lesser harm from vutrisiran in comparison with patisiran.

These specific AEs are additionally considered in the sections on the risk of bias (Section 2.3) and on the probability and extent of added benefit (Section 2.4).

A “major” effect in favour of vutrisiran is shown for the specific AE “general disorders and administration site conditions” (SAE). A total of 5 patients were affected by the heterogeneous events summarized under this specific AE (PTs "asthenia", "general physical health deterioration", "phlebitis at the infusion site", "chest pain", "heat sensation" and "swelling face"). With "phlebitis at the infusion site", a PT is included that could only be recorded in the control arm and from which 1 patient was affected. If this PT is not taken into account and the affected patient is not additionally included in the analysis with one of the other PTs, this

specific AE would affect 1 vs. 3 patients and the size of the effect would be minor. Due to this data situation, the extent of this effect is rated as non-quantifiable.

2.1.3 Severe AEs

In its comment, the company states that the severity of all AEs was specified by the investigator and an imputation of AEs as severe did thus not occur in the HELIOS-A study. Thus, one of the uncertainties described in dossier assessment A22-114 regarding this outcome is resolved. However, further uncertainties described in dossier assessment A22-114 still remain. First, only a definition corresponding to the wording of the comprehensive definition of the National Cancer Institute (NCI) Common-Terminology-Criteria-for-Adverse-Events (CTCAE) grades, which was provided in the study protocol but not in the Case Report Form (CRF), was used, but not the full CTCAE assessment system, including the specific definitions for many PTs. Furthermore, the outcome of SAEs shows a clearly less pronounced effect. The extent of the outcome "severe AEs" is therefore still assessed as unquantifiable.

2.2 Assessment of further outcomes of the HELIOS-A study

mNIS+7 and NIS

No new data were submitted in the context of the comments that change the assessment of these outcomes of the HELIOS-A study described in dossier assessment A22-114. The parameters recorded with the mNIS+7 and the NIS are not assessed as directly relevant to patients. The results of the continuous analyses of the total values of mNIS+7 and NIS at month 18 are presented as supplementary information in Appendix A. There was no statistically significant difference between the study arms.

FAP and PND

No new data were submitted in the context of the comments that change the assessment of these outcomes of the HELIOS-A study described in dossier assessment A22-114. On the one hand, the consideration of deterioration would be relevant in a progressive disease such as hATTR amyloidosis. On the other hand, the significance of a change can vary depending on the individual patient and the baseline score. The analysis of the relative risk (RR) of improvement (change to a lower FAP stage or to a lower PND value) presented by the company in the dossier is not meaningfully interpretable. The information on FAP stages and PND values provided by the company in the dossier is therefore presented without effect estimates in Appendix B as supplementary information. It is still unclear whether the PND values "IIIa" and "IIIb" were analysed as separate PND values.

R-ODS

No new data were submitted in the context of the comments that change the assessment of this outcome of the HELIOS-A study described in dossier assessment A22-114. The result of

the continuous analysis at month 18 is presented as supplementary information in Appendix C. There was no statistically significant difference between the study arms.

2.3 Risk of bias

In its comments, the company underlines that the observation period for all-cause mortality and AEs in the HELIOS-A study was 84 weeks in both study arms. Moreover, the company states that the severity of all AEs was specified by the investigator and an imputation of AEs as severe did thus not occur in the HELIOS-A study. These two aspects are thus omitted from the assessment of the risk of bias.

The risk of bias for the results of the relevant outcomes was reassessed. The table includes additional outcomes on AEs beyond those presented in A22-114 (see Section 2.1.2).

Table 2 describes the risk of bias for the results of the relevant outcomes.

Table 2: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: vutrisiran vs. patisiran

Study		Outcomes													
	Study level	All-cause mortality	Symptoms (Norfolk QoL-DN)	Symptoms (10-MWT)	Health status (EQ-5D-5L VAS)	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infusion-related reaction	Injury, poisoning and procedural complications (SOC, severe AE[a])	Infections and infestations (SOC, SAE)	Heart failure (SMQ narrow scope, SAE)	Gastrointestinal disorders (SOC, SAE)	General disorders and administration site conditions (SOC, SAE)
HELIOS-A	N	N	H[b]	H[b]	H[b]	–[c]	H[d]	H[b, d]	H[b, d]	–[e]	H[b, d]	H[d]	H[d]	H[d]	H[d]

a. Severe AEs are operationalized as severe or medically significant but not immediately life-threatening; hospitalization or prolonged stays in hospital indicated; impairing; limiting self-care in daily life (e. g. bathing, dressing and undressing, feeding, toileting, taking medication, and not confined to bed); or life-threatening consequences; urgent intervention indicated; or death due to adverse events. The wording of this definition corresponds to the criteria according to NCI-CTCAE grade ≥ 3.
b. Lack of blinding in subjective outcomes or subjective recording of outcomes.
c. Outcome not recorded; the company allocated the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) instrument to health-related quality of life.
d. Including a relevant proportion of events that can be both side effects and symptoms.
e. The analysis presented by the company is not suitable for the benefit assessment; however, the events underlying the outcome are recorded via the specific AEs.

10-MWT: 10-metre walk test; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; NCI: National Cancer Institute; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; RCT: randomized controlled trial; SMQ: Standardized MedDRA Query; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

There are no biasing aspects in the outcome of all-cause mortality, so the risk of bias for the result of this outcome is rated as low.

There is still a high risk of bias in the results on outcomes from the side effects category due to a relevant proportion of included events that can be both side effects and symptoms of the disease.

2.4 Probability and extent of added benefit

Table 3 shows probability and extent of the respective added benefit at outcome level based on the results presented in dossier assessment A22-114 and in the previous Sections 2.1 and 2.3.

Table 3: Extent of added benefit at outcome level: vutrisiran versus patisiran (multipage table)

Outcome category **outcome**	**Vutrisiran vs. patisiran** **proportion of events (%) or LS mean** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	1.6% vs. 7.1% RR 0.23 [0.04; 1.33] p = 0.078	Lesser/added benefit not proven
Morbidity		
Symptoms (Norfolk QoL-DN[c])	0.9 vs. 3.6 LS MD: -2.7 [-9.2; 3.7] p = 0.401	Lesser/added benefit not proven
Symptoms (10-MWT [m/s])	-0.03 vs. -0.07 LS MD: 0.04 [-0.06; 0.14] p = 0.441	Lesser/added benefit not proven
Health status (EQ-5D-5L VAS[d])	-0.5 vs. -5.3 LS MD: 4.8 [-0.3; 9.9] p = 0.067	Lesser/added benefit not proven
Health-related quality of life		
Outcome not recorded[e]		
Side effects[f]		
SAEs	26.2% vs. 42.9% RR: 0.61 [0.39; 0.97] p = 0.045 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm; extent: "minor"
Severe AEs	15.6% vs. 38.1% RR: 0.41 [0.23; 0.72] p = 0.002 probability: “hint”	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"
Discontinuation due to AEs	2.5% vs. 7.1% RR: 0.34 [0.07; 1.64] p = 0.174	Greater/lesser harm not proven

Table 3: Extent of added benefit at outcome level: vutrisiran versus patisiran (multipage table)

Outcome category **outcome**	**Vutrisiran vs. patisiran** **proportion of events (%) or LS mean** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Infusion-related reaction	Analysis unsuitable[g]	Greater/lesser harm not proven
Injury, poisoning and procedural complications (severe AEs)	0.8% vs. 7.1% RR: 0.12 [0.01; 1.07] p = 0.031 probability: “hint”	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"
Infections and infestations (SAEs)	7.4% vs. 19.0% RR: 0.39 [0.16; 0.94] p = 0.034 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm; extent: "minor"
Cardiac failure (SAE)	3.3% vs. 11.9% RR: 0.28 [0.08; 0.98] p = 0.036 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm; extent: "minor"
Gastrointestinal disorders (SAEs)	0.8% vs. 7.1% RR: 0.11 [0.01; 1.07] p = 0.031 probability: “hint”	Outcome category: serious/severe side effects lesser harm, extent: "minor"[h]
General disorders and administration site conditions (SUE)	0.8% vs. 9.5% RR: 0.09 [0.01; 0.749] p = 0.008 probability: “hint”	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. Lower values indicate fewer symptoms (scale range -4 to 136). Negative effects (vutrisiran versus patisiran) indicate an advantage for the intervention.
d. Higher values mean a better health status (scale range 0 to 100). Positive effects (vutrisiran versus patisiran) indicate an advantage for the intervention.
e. Outcome not recorded; the company allocated the Norfolk QoL-DN instrument to health-related quality of life.
f. Includes events which can be both side effects and symptoms of the disease.
g. The analysis presented by the company is not suitable for the benefit assessment; however, the events underlying the outcome are recorded via the specific AEs.
h. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods; the extend is rated as “minor”.

10-MWT: 10-metre walk test; AE: adverse event: CI: confidence interval; CI_u: upper limit of the confidence interval; CI_L: lower limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; LS: least squares; MD: mean difference; NCI: National Cancer Institute; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

Table 4 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 4: Positive and negative effects from the assessment of vutrisiran in comparison with patisiran

Positive effects	**Negative effects**
Serious/severe side effects[a] ▪ SAEs: hint of lesser harm – extent: “minor” ▫ infections and infestations: hint of lesser harm - extent “minor” ▫ cardiac failure: hint of lesser harm – extent: “minor” ▫ gastrointestinal disorders: hint of lesser harm – extent: "minor" ▫ general disorders and administration site conditions: hint of lesser harm – extent: "non-quantifiable" ▪ severe AEs: hint of lesser harm - extent: “non-quantifiable” ▫ injury, poisoning and procedural complications (severe AEs): hint of lesser harm - extent: "non-quantifiable"	–
There are no data on the outcome of health-related quality of life	
a. Includes events which can be both side effects and symptoms of the disease. AE: adverse event; SAE: serious adverse event	

The overall consideration yields positive effects of vutrisiran over patisiran for the outcomes of SAEs and severe AEs. Events may be included that can be assigned to both side effects and symptoms of the disease.

In summary, there is a hint of minor added benefit of vutrisiran over patisiran for patients with hATTR amyloidosis with stage 1 or stage 2 polyneuropathy.

2.5 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of vutrisiran from dossier assessment A22-114.

The following Table 5 shows the result of the benefit assessment of vutrisiran taking into account both dossier assessment A22-114 and the present addendum.

Table 5: Vutrisiran – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with hATTR amyloidosis with stage 1 or stage 2 polyneuropathy[b]	Tafamidis (only for hATTR amyloidosis with stage 1 polyneuropathy) or **patisiran**[c]	Hint of minor added benefit[d]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. It is assumed that liver transplantation is not an option at the time of therapy with vutrisiran.
c. It is assumed that a patient-specific adequate treatment of the respective organ manifestation (such as cardiac failure and/or polyneuropathy) corresponding to the state of medical knowledge is carried out in both study arms, taking into account the special features of the disease hAATR amyloidosis, and is documented as concomitant treatment.
d. The HELIOS-A study included only patients with a KPS ≥ 60% and an NYHA classification ≤ II. It remains unclear whether the observed effects are transferable to patients with a KPS < 60 or an NYHA classification > II.

G-BA: Federal Joint Committee; hATTR amyloidosis: hereditary transthyretin amyloidosis; KPS: Karnofsky performance status; NYHA: New York Heart Association

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

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Appendix A Results on mNIS+7 and NIS

Table 6: Results on mNIS+7 und NIS – RCT, direct comparison: vutrisiran versus patisiran

Study outcome	Vutrisiran			Patisiran			Vutrisiran vs. patisiran
	N[a]	values at baseline mean (SD)	change at month 18 LS mean[b] (SE)	N[a]	values at baseline mean (SD)	change at month 18 LS mean[b] (SE)	LS MD [95% CI]; p-value[c]
HELIOS-A							
mNIS +7 total score[d]	115	60.6 (36.0)	0.7 (1.6)	36	57.7 (33.7)	1.4 (2.8)	-0.8 [-7.0; 5.4]; 0.808
NIS total value[e]	115	43.0 (28.6)	2.7 (1.3)	36	43.1 (28.2)	2.3 (2.2)	0.4 [-4.6; 5.5]; 0.871

a. Number of patients considered in the analysis to calculate the effect estimation; the values at baseline are based on 122 patients in the intervention arm and 42 patients in the control arm.
b. From the MMRM analysis.
c. Effect, CI and p-values: MMRM with unstructured variance matrix, baseline value as continuous covariable, treatment, visit, genotype, age at onset of disease and NIS at baseline (< 50 vs. ≥ 50) as categorical factors, interaction term treatment × visit. Effect refers to the change from baseline at the time point 18 months.
d. Lower values indicate minor symptoms (scale range 0 to 304). Negative effects (vutrisiran versus patisiran) indicate an advantage for the intervention.
e. Lower values indicate minor symptoms (scale range 0 to 244). Negative effects (vutrisiran versus patisiran) indicate an advantage for the intervention.

CI: confidence interval; LS: least squares; MD: mean difference; MMRM: mixed-effects model repeated measures; mNIS+7: modified Neuropathy Impairment Score +7; N: number of analysed patients; NIS: Neuropathy Impairment Score; RCT: randomized controlled trial; SD: standard deviation; SE: standard error

Appendix B Results on FAP and PND

Table 7: Results on FAP and PND – RCT, direct comparison: vutrisiran versus patisiran

Study	Vutrisiran					Patisiran				
outcome	N	improvement[a] n (%)	stabilisation[b] n (%)	deterioration[c] n (%)	missing values n (%)	N	improvement[a] n (%)	stabilisation[b] n (%)	deterioration[c] n (%)	missing values n (%)
HELIOS-A										
FAP	122	5 (4.1)	101 (82.8)	9 (7.4)	7 (5.7)	42	1 (2.4)	36 (85.7)	1 (2.4)	4 (9.5)
PND	122	13 (10.7)	82 (67.2)	20 (16.4)	7 (5.7)	42	1 (2.4)	30 (71.4)	7 (16.7)	4 (9.5)

a. Lower FAP stage or lower PND score at month 18 compared to baseline.

b. Same FAP stage or same PND score at month 18 compared to baseline.

c. Higher FAP stage or higher PND score at month 18 compared to baseline.

FAP: Familial Amyloidotic Polyneuropathy; n: number of patients in the category; N: number of randomized patients; PND: polyneuropathy disability; RTC: randomized controlled trial

Appendix C Results on the R-ODS

Table 8: Results on the R-ODS, direct comparison: vutrisiran versus patisiran

Study outcome	Vutrisiran			Patisiran			Vutrisiran vs. patisiran
	N[a]	values at baseline mean (SD)	change at month 18 LS mean[b] (SE)	N[a]	values at baseline mean (SD)	change at month 18 LS mean[b] (SE)	LS MD [95% CI]; p-value[c]
HELIOS-A							
R-ODS[d]	114	34.1 (11.0)	-1.8 (0.5)	38	34.0 (10.4)	-2.1 (0.9)	0.2 [-1.7; 2.2]; 0.809

a. Number of patients considered in the analysis to calculate the effect estimation; the values at baseline are based on 122 patients in the intervention arm and 42 patients in the control arm.
b. From the MMRM analysis.
c. Effect, CI and p-values: MMRM with unstructured variance matrix, baseline value as continuous covariable, treatment, visit, genotype, age at onset of disease and NIS at baseline (< 50 vs. ≥ 50) as categorical factors, interaction term treatment × visit. Effect refers to the change from baseline at the time point 18 months.
d. Higher values indicate minor symptoms (scale range 0 to 48). Positive effects (vutrisiran versus patisiran) indicate an advantage for the intervention.

CI: confidence interval; LS: least squares; MD: mean difference; MMRM: mixed-effects model repeated measures; mNIS+7: modified Neuropathy Impairment Score +7; N: number of analysed patients; NIS: Neuropathy Impairment Score; RCT: randomized controlled trial; SD: standard deviation; SE: standard error

Appendix D Results on side effects

Table 9: Common AEs[a] – RCT, direct comparison: vutrisiran vs. patisiran (multipage table)

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**vutrisiran N = 122**	**patisiran N = 42**
HELIOS-A		
Overall AE rate	119 (97.5)	41 (97.6)
Cardiac disorders	37 (30.3)	**11 (26.2)**
Eye disorders	35 (28.7)	10 (23.8)
Gastrointestinal disorders	49 (40.2)	**20 (47.6)**
Abdominal pain	11 (9.0)	1 (2.4)
Diarrhoea	17 (13.9)	7 (16.7)
Nausea	12 (9.8)	**5 (11.9)**
General disorders and administration site conditions	48 (39.3)	**14 (33.3)**
Oedema peripheral	16 (13.1)	4 (9.5)
Immune system disorders	3 (2.5)	10 (23.8)
Infusion-related reaction[c]	0 (0)	10 (23.8)
Infections and infestations	67 (54.9)	25 (59.5)
Urinary tract infection	16 (13.1)	8 (19.0)
Injury, poisoning and procedural complications	54 (44.3)	16 (38.1)
Fall	22 (18.0)	6 (14.3)
Investigations	25 (20.5)	9 (21.4)
Metabolism and nutrition disorders	15 (12.3)	6 (14.3)
Musculoskeletal and connective tissue disorders	56 (45.9)	17 (40.5)
Back pain	**6 (4.9)**	**6 (14.3)**
Arthralgia	13 (10.7)	4 (9.5)
Pain in an extremity	18 (14.8)	**4 (9.5)**
Nervous system disorders	54 (44.3)	**18 (42.9)**
Dizziness	13 (10.7)	**1 (2.4)**
Headache	11 (9.0)	**6 (14.3)**
Syncope	12 (9.8)	1 (2.4)
Psychiatric disorders	20 (16.4)	4 (9.5)
Renal and urinary disorders	17 (13.9)	9 (21.4)
Reproductive system and breast disorders	12 (9.8)	1 (2.4)
Respiratory, thoracic and mediastinal disorders	29 (23.8)	7 (16.7)
Skin and subcutaneous tissue disorders	39 (32.0)	**14 (33.3)**
Vascular disorders	18 (14.8)	**12 (28.6)**

Table 9: Common AEs[a] – RCT, direct comparison: vutrisiran vs. patisiran (multipage table)

Study	**Patients with event n (%)**	
SOC[b]	**vutrisiran**	**patisiran**
PT[b]	**N = 122**	**N = 42**

a. Events that occurred in ≥ 10 patients in the intervention arm or in ≥ 10% of the patients in the comparator arm; during the 18-month randomized treatment phase of vutrisiran vs. patisiran (until week 84); includes events which can be both side effects and symptoms of the disease; changes in comparison with A22-114 are printed in **bold**.
b. MedDRA version 23.0; SOCs and PTs used unmodified from Module 4 A.
c. The company did not assign the PT "infusion-related reactions" to the primary SOC "injury, poisoning and procedural complications", but to the SOC "immune system disorders".

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 10: Common SAEs[a] – RCT, direct comparison: vutrisiran vs. patisiran

Study	**Patients with event n (%)**	
SOC[b]	**vutrisiran**	**patisiran**
PT[b]	**N = 122**	**N = 42**
HELIOS-A		
Total SAE rate	32 (26.2)	18 (42.9)
Cardiac disorders	11 (9.0)	6 (14.3)
Immune system disorders	0 (0)	3 (7.1)
Infusion-related reaction[c]	0 (0)	3 (7.1)
Infections and infestations	9 (7.4)	8 (19.0)
Cellulitis at the infusion site	0 (0)	3 (7.1)
Gastrointestinal disorders	**1 (0.8)**	**3 (7.1)**
General disorders and administration site conditions	**1 (0.8)**	**4 (9.5)**

a. Events that occurred in ≥ 5% of the patients in at least 1 study arm; during the 18-month randomized treatment phase of vutrisiran vs. patisiran (until week 84); includes events which can be both side effects and symptoms of the disease; changes in comparison with A22-114 are printed in **bold**.
b. MedDRA version 23.0; SOCs and PTs used unmodified from Module 4 A.
c. The company did not assign the PT "infusion-related reactions" to the primary SOC "injury, poisoning and procedural complications", but to the SOC "immune system disorders".

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class