Appendices

Appendix Table 1: Research questions and corresponding publicly available non-AMNOG documents considered in the analysis

Project [reference]	Research question (PIC: patients, intervention, comparator)	Study	Intervention	Comparator	Relevant population	Journal publication [reference]	Registry report [reference]	EPAR [reference]
A11-02 [1-3]	Ticagrelor versus clopidogrel in patients with unstable angina pectoris and myocardial infarction without ST-segment elevation (unstable angina/NSTEMI)	D5130C05262 (PLATO)	Ticagrelor + acetylsalicylic acid	Clopidogrel + acetylsalicylic acid	Subpopulation[a]	[4-11]	[12] NCT00391872 No results posted	[13]
	Ticagrelor versus prasugrel in patients with myocardial infarction with ST-segment elevation (STEMI) in whom a percutaneous coronary intervention (PCI) had been performed	D5130C05262 (PLATO)	Ticagrelor + acetylsalicylic acid	Prasugrel + acetylsalicylic acid	Subpopulation[a]	[4-11]	[12] NCT00391872 No results posted	[13]
		TRITON-TIMI 38 (TRITON)	Ticagrelor + acetylsalicylic acid	Prasugrel + acetylsalicylic acid	Subpopulation[b]	[14-26]	[27] NCT00097591 Results posted	[28]
A11-17 [29-31]	Boceprevir + pegylated interferon alfa in combination with ribavirin versus pegylated interferon alfa in combination with ribavirin in patients with chronic HCV infection, genotype 1, treatment-naïve patients without cirrhosis	SPRINT-2	Boceprevir + pegylated interferon alfa + ribavirin	Pegylated interferon alfa + ribavirin	Study population	[32]	[33] NCT00705432 Results posted	[34]
	Boceprevir + pegylated interferon alfa in combination with ribavirin versus pegylated interferon alfa in combination with ribavirin in patients with chronic HCV infection, genotype 1, treatment-experienced patients without cirrhosis	RESPOND-2	Boceprevir + pegylated interferon alfa + ribavirin	Pegylated interferon alfa + ribavirin	Study population	[35]	[36] NCT00708500 Results posted	[34]

Project [reference]	Research question (PIC: patients, intervention, comparator)	Study	Intervention	Comparator	Relevant population	Journal publication [reference]	Registry report [reference]	EPAR [reference]
A11-20 [37-39]	Abiraterone versus BSC in patients with metastatic, hormone-refractory prostate cancer who show progression during or after docetaxel-containing chemotherapy and for whom further treatment with docetaxel is no longer an option.	COU-AA-301	Abiraterone acetate + prednisone	Palliative treatment with dexamethasone, prednisone, prednisolone or methylprednisolone, as well as best supportive care (e.g. adequate pain therapy).	Study population	[40]	[41-44] NCT00638690 No results posted	[45]
A11-23 [46-48]	Fingolimod versus beta-interferon (im) in patients with rapidly evolving severe relapsing-remitting multiple sclerosis	TRANSFORMS (CFTY720D2302)	Fingolimod	beta-interferon, i.m.	Subpopulation[c]	[49]	[50] NCT00340834 No results posted	[51]
A11-24 [52-54]	Cabazitaxel versus BSC in patients with metastatic, hormone-refractory prostate cancer who show progression during or after docetaxel-containing chemotherapy and for whom further treatment with docetaxel is no longer an option.	TROPIC	Cabazitaxel + prednisone or prednisolone	Palliative treatment with dexamethasone, prednisone, prednisolone or methylprednisolone, as well as best supportive care (e.g. adequate pain therapy).	Study population	[55]	[56 57] NCT00417079 Results posted	[58]
A11-25 [37 59 60]	Telaprevir in a response-guided treatment regimen versus pegylated interferon alfa in combination with ribavirin in patients with chronic HCV infection (treatment-naïve patients without cirrhosis).	ADVANCE	Telaprevir in a response-guided treatment regimen	Pegylated interferon alfa + ribavirin	Study population	[61]	[62] NCT00627926Results posted	[63]

Project [reference]	Research question (PIC: patients, intervention, comparator)	Study	Intervention	Comparator	Relevant population	Journal publication [reference]	Registry report [reference]	EPAR [reference]
		G060-A6	Telaprevir in a response-guided treatment regimen	Pegylated interferon alfa + ribavirin	Study population	[64]	[65] NCT00780416 No results posted	[63]
	Telaprevir treatment in a regimen with fixed duration of treatment (48 weeks) versus pegylated interferon alfa in combination with ribavirin in patients with chronic HCV infection (previously treated patients – non-responders with or without cirrhosis)	REALIZE	Telaprevir treatment in a regimen with fixed duration of treatment (48 weeks)	Pegylated interferon alfa + ribavirin	Study population	[66]	[67] NCT00703118 Results posted	[63]
	Telaprevir treatment in a regimen with fixed duration of treatment (48 weeks) versus pegylated interferon alfa in combination with ribavirin in patients with chronic HCV infection (previously treated patients – relapsed patients with cirrhosis)	REALIZE	Telaprevir treatment in a regimen with fixed duration of treatment (48 weeks)	Pegylated interferon alfa + ribavirin	Study population	[66]	[67] NCT00703118 Results posted	[63]
A11-26 [68-70]	Eribulin versus monotherapy with capecitabine, 5-fluorouracil, vinorelbine in patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease (patients in whom further treatment with taxanes is still possible).	EMBRACE	Eribulin	Treatment containing an anthracycline or taxane	Subpopulation[d]	[71]	[72] NCT00388726 No results posted	[73]
	Eribulin versus monotherapy with capecitabine, 5-fluorouracil, vinorelbine in patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease (patients for whom treatment with taxanes or anthracyclines is no longer an option).	EMBRACE	Eribulin	Monotherapy with capecitabine, 5-fluorouracil, vinorelbine	Subpopulation[d]	[71]	[72] NCT00388726 No results posted	[73]

Project [reference]	Research question (PIC: patients, intervention, comparator)	Study	Intervention	Comparator	Relevant population	Journal publication [reference]	Registry report [reference]	EPAR [reference]
A11-30 [74-76]	Apixaban versus enoxaparin in adult patients after elective hip replacement surgery	ADVANCE-3	Apixaban	Enoxaparin	Study population	[77]	[78] NCT00423319 No results posted	[79]
	Apixaban versus enoxaparin in adult patients after elective knee replacement surgery	ADVANCE-2	Apixaban	Enoxaparin	Study population	[80]	[81] NCT00452530 No results posted	[79]
A12-03 [82-84]	Belatacept versus ciclosporin for the prophylaxis of graft rejection in adults receiving a renal transplant from a donor classified according to standard criteria (SCD)	IM103008 (BENEFIT)	Belatacept	Ciclosporin A	Study population	[85-87]	[88 89] NCT00256750 No results posted	[90]
	Belatacept versus ciclosporin for the prophylaxis of graft rejection in adults receiving a renal transplant from a donor classified according to extended criteria (ECD)	IM103027 (BENEFIT-EXT)	Belatacept	Ciclosporin A	Study population	[85 91]	[92 93] NCT00114777 No results posted	[90]
A12-04 [94-96]	Rilpivirine in combination with other antiretroviral drugs versus efavirenz in combination with other antiretroviral drugs for treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml	TMC278-C204	Rilpivirine	Efavirenz	Subpopulation[e]	[97]	[98] NCT00110305 No results posted	[99]
		TMC278-TIDP6-C209 (ECHO)	Rilpivirine	Efavirenz	Subpopulation[e]	[100]	[101] NCT00540449 Results	[99]

Project [reference]	Research question (PIC: patients, intervention, comparator)	Study	Intervention	Comparator	Relevant population	Journal publication [reference]	Registry report [reference]	EPAR [reference]
							posted	
		TMC278-TIDP6-C215 (THRIVE)	Rilpivirine	Efavirenz	Subpopulation[e]	[102]	[103] NCT00543725 Results posted	[99]
A12-07 [104-106]	Ipilimumab versus BSC in adult patients with advanced (unresectable or metastatic) melanoma, who have received prior therapy	MDX010-20	Ipilimumab	Best supportive care	Study population	[107]	[108 109] NCT00094653 Results posted	[110]
A12-08 [111-113]	Vemurafenib versus dacarbazine in the treatment of adult patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma	BRIM-3	Vemurafenib	Dacarbazine	Study population	[114]	[115] NCT01006980 Results posted	[116]
A12-02/10 [117-119]	Rilpivirine/emtricitabine/tenofovir (fixed-dose combination) versus efavirenz in combination with emtricitabine/tenofovir or in combination with abacavir/lamivudine for the treatment of human immunodeficiency virus type 1 HIV-1 infection in antiretroviral-naïve adult patients with a viral load of ≤ 100,000 HIV-1 RNA copies/ml	TMC278-C204	Rilpivirine/emtricitabine/ tenofovir	Efavirenz + emtricitabine/tenofovir or + abacavir/lamivudine	Subpopulation[e]	[97]	[98] NCT00110305 No results posted	[99]
		TMC278-TIDP6-C209 (ECHO)	Rilpivirine/emtricitabine/ tenofovir	Efavirenz + emtricitabine / tenofovir or +abacavir /	Subpopulation[e]	[100]	[101] NCT00540449	[99]

Project [reference]	Research question (PIC: patients, intervention, comparator)	Study	Intervention	Comparator	Relevant population	Journal publication [reference]	Registry report [reference]	EPAR [reference]
				lamivudine			Results posted	
		TMC278-TIDP6-C215 (THRIVE)	Rilpivirine/emtricitabine/ tenofovir	Efavirenz + emtricitabine / tenofovir or +abacavir / lamivudine	Subpopulation[e]	[102]	[103] NCT00543725 Results posted	[99]
A12-14 [74 120 121]	Axitinib versus sorafenib in patients with advanced metastatic RCC in adult patients after failure of prior treatment with cytokines	AXIS (A4061032)	Axitinib (after failure of prior treatment)	Sorafenib (after failure of prior treatment)	Subpopulation[f]	[122]	[123 124] NCT00678392 Results posted	[125]
A12-15 [126-128]	Crizotinib versus docetaxel or pemetrexed in patients with previously treated ALK-positive advanced NSCLC in whom chemotherapy is indicated (in particular, these can be patients with ECOG performance status 0, 1, and, if applicable, 2)	PROFILE 1007	Crizotinib	Docetaxel or pemetrexed	Study population	-	[129] NCT00932893 No results posted	[130]
15 projects	22 different research questions	22 studies[g]			Study population (15) subpopulation (13)	42	22 registry reports[g], 11 with results[h]	15

a: Restriction of acetylsalicylic acid co-medication to a maximum dose of 150 mg.
b: According to the SPC, patients ≥ 75 years, with a body weight of < 60 kg, as well as those with a stroke / TIA in the medical history must have been excluded from the analysis.
c: Population is restricted to patients with prior treatment with IFN-β and a high or very high disease activity.
d: Population is restricted to patients receiving the ACT (various other treatments were allowed in the comparator arm).
e: Population is restricted to patients with a viral load of ≤ 100,000 HIV-1 RNA copies/ml.
f: Population is restricted to patients previously treated with a cytokine, because the study comparator is the ACT only for this subpopulation.

Project [reference]	Research question (PIC: patients, intervention, comparator)	Study	Intervention	Comparator	Relevant population	Journal publica-tion [referen-ce]	Registry report [referen-ce]	EPAR [refer ence]
g: Six of these studies referred to 2 research questions each. h: Three of these studies referred to 2 research questions each. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; AMNOG: Arzneimittelmarktneuordnungsgesetz (Act on the Reform of the Market for Medicinal Products); BSC: best supportive care; ECD: extended criteria donors; ECOG: Eastern Cooperative Oncology Group; EPAR: European public assessment report; HCV: hepatitis C virus; HIV-1: human immunodeficiency virus type 1; IFN-β: interferon-β; im: intramuscular; NSCLC; non-small cell lung cancer; NSTEMI: myocardial infarction without ST-segment elevation; PCI: percutaneous coronary intervention; PIC: patients / indication / comparator; RCC: renal cell carcinoma; SCD: standard criteria donors; SPC: summary of product characteristics; STEMI: myocardial infarction with ST-segment elevation								

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Appendix Table 2: Coding of study methods items

	Completely reported including numerical data	**Partly reported including numerical data**	**Not reported**[a]
Randomisation	▪ Study is identified as randomised, method for generation of code is available (e.g. computer generated list)	▪ Study is identified as randomised, but no information on randomisation procedures available	▪ No information on randomisation available
Allocation concealment	▪ One of the following procedures described: treatment allocation by telephone or IVRS, use of identical numbered boxes, use of sealed opaque envelopes	▪ Incomplete or unclear information on allocation concealment	▪ No information on allocation concealment available
Blinding	▪ study identified as (double) blinded, blinded parties (e.g. investigator, patient, outcome assessor) identified and ▪ methods of blinding described, e.g. use of matching placebo or double-dummy technique or ▪ study identified as open label	▪ Study identified as (double) blinded, but blinded parties or method of blinding not described	▪ No information on blinding available
Definition of ITT data set	▪ Analysis data set identified as ITT, including an adequate definition (according to ICH E9)	▪ Not applicable	▪ No information on analysis data set available; ▪ analysis data set identified as ITT without definition of ITT ▪ analysis data set not meeting requirements of ITT analysis
Patient number in ITT data set	▪ Adequate definition of ITT data set and number of patients in ITT analysis available ▪ no ITT definition available but analysis data set includes at least 95% of randomised patients	▪ Number of patients in ITT data set available only for some endpoints	▪ No definition of analysis data set available and number of patients in analysis is not stated ▪ exclusion of patients from ITT data set not justified ▪ ITT data set reported but, however, number

	Completely reported including numerical data	**Partly reported including numerical data**	**Not reported[a]**
			of randomised patients or number of patients excluded from analysis not available or < 95% of the randomised patients analysed
Intervention (regarding to dose, route, timing, duration, concurrent medication[b])	▪ Exact definition on how to carry on intervention (separate for each of the defined items)	▪ Incomplete or unclear definition on how to carry on intervention	▪ No definition on how to carry on intervention
Comparator (regarding to dose, route, timing, duration, concurrent medication[b])	▪ Exact definition on how to carry on comparator	▪ Incomplete or unclear definition on how to carry on comparator	▪ No definition on how to carry on intervention
Definition of outcome	▪ Exact definition for every single outcome (e.g. diagnostic method, units, cut-offs, scales etc.)	▪ Incomplete or unclear information on outcome	▪ No information on outcome definition

a: If a document was not publicly available each item was coded as "not reported".
b: Coding was done separately for each of the named items.
ICH: International Conference on Harmonisation, ITT: intention to treat, IVRS: Interactive Voice Response System

Appendix Table 3: Coding of study results items (baseline characteristics and patient-relevant outcomes)

Results	**Completely reported including numerical data**	**Partly reported including numerical data**	**Verbally reported without numerical data**	**Not reported[a]**
Baseline characteristics (age)	▪ Measure of location and measure of variation (e.g. mean value and CI or SE)	▪ Mean value and measure of variation (e.g. mean value and CI or SE)	▪ Not applicable	▪ No information
Baseline characteristics (gender)	▪ Number of patients according to gender	▪ Not applicable	▪ Not applicable	▪ No information
Baseline characteristics (severity)[b]	▪ Mean value and measure of variation (e.g. mean value and CI or SE) or number of patients	▪ Mean value and measure of variation (e.g. mean value and CI or SE)	▪ Not applicable	▪ No information
General definitions on outcomes	continuous data (for ITT analysis): ▪ for end-of-study value or for change from baseline: estimated effect size and measure of variation (e.g. mean value and CI or SE) categorical data (for ITT analysis): ▪ number of patients with events and % of analysis data set per group ▪ % not required if total number of patients in analysis data set clearly available	▪ Any of the items of full reporting missing ▪ data insufficient to be included in meta-analysis (without derivation of data, e.g. of variance from p-values)	▪ Verbal reporting of statistical significance of group difference (statistically significant / not statistically significant)	▪ No information on outcome ▪ verbal description with information on statistical significance of group difference (e.g. “no differences”, “comparable results”) ▪ results only available graphically in a figure without reporting of exact numerical data
Additional specific definitions:				
Patients with AEs		▪ Reporting of the % of patients with AEs without the number of patients affected by AEs		▪ Reporting of numbers of AEs without the number of patients affected by AE
Patients with AEs of special interest		▪ Reporting of the % of patients with AEs of special interest without the number of patients affected by AEs of special interest		▪ Reporting of numbers of AEs of special interest without the number of patients affected by AE of special interest

Results	**Completely reported including numerical data**	**Partly reported including numerical data**	**Verbally reported without numerical data**	**Not reported[a]**
Patients with SAEs		▪ Reporting of the % of patients with SAEs without the number of patients affected by SAEs		▪ Reporting of SAEs without the number of patients affected by SAEs
Patients withdrawn due to AE		▪ Reporting of the % of patients withdrawn due to AEs without the number of patients withdrawn due to AEs		▪ Reporting of AEs resulting in withdrawal without the number of patients withdrawn due to AEs
a: If a document was not (publicly) available ,each item was coded as "not reported". b: Results on severity were only collected if they were relevant for the given indication. AE: adverse event; CI: confidence interval; ITT: intention to treat; SAE: serious adverse event; SE: standard error				

Appendix Table 4: Rates of complete information on study methods (by document type and relevant population for approval) – Inclusion of registry reports with results

Information	Complete study information by item and document type											
	Total study population relevant[a] n (%)						Subpopulation relevant[b] n (%)					
	No. of exp. items[c]	AMNOG[d]	EPAR	Publication	Registry report	Non-AMNOG total	No. of exp. items[e]	AMNOG[d]	EPAR	Publication	Registry report	Non-AMNOG total
Study methods (individual items and item categories)												
Randomisation	8	8 (100)	3 (38)	7 (88)	2 (25)	8 (100)	6	5 (83)	6 (100)	6 (100)	0 (0)	6 (100)
Allocation concealment	8	8 (100)	3 (38)	7 (88)	0 (0)	8 (100)	6	5 (83)	3 (50)	5 (83)	0 (0)	5 (83)
Blinding	8	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	6	5 (83)	6 (100)	3 (50)	5 (83)	6 (100)
Definition of ITT dataset	8	8 (100)	7 (88)	8 (100)	3 (38)	8 (100)	6	6 (100)	6 (100)	3 (50)	1 (17)	6 (100)
No of patients in ITT dataset	8	8 (100)	6 (75)	6 (75)	3 (38)	6 (75)	6	6 (100)	4 (67)	3 (50)	3 (50)	4 (67)
Subtotal risk of Bias items	**40**	**40 (100)**	**27 (68)**	**36 (90)**	**16 (40)**	**38 (95)**	**30**	**27 (90)**	**25 (83)**	**20 (67)**	**9 (30)**	**27 (90)**
Intervention[f]	36	36 (100)	36 (100)	36 (100)	36 (100)	36 (100)	30	29 (97)	28 (93)	28 (93)	24 (80)	30 (100)
Comparator[f]	32	32 (100)	23 (72)	31 (97)	31 (97)	31 (97)	30	29 (97)	28 (93)	27 (90)	24 (80)	30 (100)
Methods of outcome measurement	74	63 (85)	26 (35)	43 (58)	33 (45)	49 (66)	73	49 (67)	31 (42)	28 (38)	33 (45)	45 (62)
Study methods total	**182**	**171 (94)**	**112 (62)**	**146 (80)**	**116 (64)**	**154 (85)**	**163**	**134 (82)**	**112 (69)**	**103 (63)**	**90 (55)**	**132 (81)**

a: Original study population investigated in the clinical studies.

b: Subpopulation of the clinical study covering the approved patient population or reflecting the patient population treated with the ACT.

c: Total number (100%) of methods items expected to be reported per document type for the 8 individual assessments of total study populations (items required according to CONSORT) for which results in registry reports are available.

d: IQWiG dossier assessment and publicly available parts of the company dossier.

e: Total number (100%) of methods items expected to be reported per document type for the 6 individual assessments of subpopulations (items required according to CONSORT) for which results in registry reports are available.

f: Includes information on dosage, intervals of administration, duration of treatment, route of administration, and concomitant medication

AMNOG: Arzneimittelmarktneuordnungsgesetz (Act on the Reform of the Market for Medicinal Products); EPAR: European public assessment report; exp.: expected; ITT: intention to treat

Appendix Table 5: Rates of complete information on baseline characteristics and patient-relevant outcomes (by document type and relevant population for approval) – Inclusion of registry reports with results

Information	Complete study information by item and document type											
	Total study population relevant[a] n (%)						Subpopulation relevant[b] n (%)					
	No. of exp. items[c]	AMNOG[d]	EPAR	Publication	Registry report	Non-AMNOG total	No. of exp. items[e]	AMNOG[d]	EPAR	Publication	Registry report	Non-AMNOG total
Study results (individual items and item categories)												
Baseline characteristics												
Age	8	8 (100)	7 (88)	6 (75)	6 (75)	8 (100)	6	3 (50)	0 (0)	1 (17)	1 (17)	1 (17)
Sex	7	7 (100)	7 (100)	7 (100)	7 (100)	7 (100)	6	6 (100)	0 (0)	1 (17)	1 (17)	1 (17)
Severity	4	4 (100)	4 (100)	4 (100)	1 (25)	4 (100)	5	3 (60)	0 (0)	0 (0)	0 (0)	0 (0)
Total baseline characteristics	**19**	**19 (100)**	**18 (95)**	**17 (89)**	**14 (74)**	**19 (100)**	**17**	**12 (71)**	**0 (0)**	**2 (12)**	**2 (12)**	**2 (12)**
Benefit outcomes												
Mortality	8	8 (100)	3 (38)	5 (63)	3 (38)	5 (63)	7	7 (100)	0 (0)	0 (0)	1 (14)	1 (14)
Clinical event[f]	5	5 (100)	5 (100)	4 (80)	3 (60)	5 (100)	7	7 (100)	3 (43)	1 (14)	0 (0)	4 (57)
Symptom[g]	4	3 (75)	0 (0)	0 (0)	0 (0)	0 (0)	5	1 (20)	0 (0)	0 (0)	0 (0)	0 (0)
HRQoL	7	3 (43)	0 (0)	0 (0)	1 (14)	1 (14)	5	5 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Subtotal benefit outcomes	**24**	**19 (79)**	**8 (33)**	**9 (38)**	**7 (29)**	**11 (46)**	**24**	**20 (83)**	**3 (13)**	**1 (4)**	**1 (4)**	**5 (21)**
Harm outcomes												
AEs	8	7 (88)	2 (25)	4 (50)	8 (100)	8 (100)	6	6 (100)	0 (0)	0 (0)	0 (0)	0 (0)
SAEs	8	7 (88)	2 (25)	3 (38)	6 (75)	6 (75)	6	5 (83)	0 (0)	0 (0)	0 (0)	0 (0)
Withdrawals due to AEs	8	7 (88)	3 (38)	4 (50)	3 (38)	5 (63)	6	5 (83)	0 (0)	0 (0)	0 (0)	0 (0)
Specific AEs[h]	26	22 (85)	2 (8)	6 (23)	4 (15)	10 (38)	31	15 (48)	0 (0)	0 (0)	0 (0)	0 (0)
Subtotal harm outcomes	**50**	**43 (86)**	**9 (18)**	**17 (34)**	**21 (42)**	**29 (58)**	**49**	**31 (63)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**

Complete study information by item and document type

Information	Total study population relevant[a] n (%)						Subpopulation relevant[b] n (%)					
	No. of exp. items[c]	AMNOG[d]	EPAR	Publication	Registry report	Non-AMNOG total	No. of exp. items[e]	AMNOG[d]	EPAR	Publication	Registry report	Non-AMNOG total
Total benefit / harm outcomes	**74**	**62 (84)**	**17 (23)**	**26 (35)**	**28 (38)**	**40 (54)**	**73**	**51 (70)**	**3 (4)**	**1 (1)**	**1 (1)**	**5 (7)**
Total study results	**93**	**81 (87)**	**35 (38)**	**43 (46)**	**42 (45)**	**59 (63)**	**90**	**63 (70)**	**3 (3)**	**3 (3)**	**3 (3)**	**7 (8)**

a: Original study population investigated in the clinical studies.
b: Subpopulation of the clinical study covering the approved patient population or reflecting the patient population treated with the ACT.
c: Total number (100%) of results items expected to be reported per document type for the 8 individual assessments of total study populations (based on characteristics and patient-relevant outcomes planned and reported in the clinical study reports, including protocols) for which results in registry reports are available.
d: IQWiG dossier assessment and publicly available parts of the company dossier.
e: Total number (100%) of results items expected to be reported per document type for the 6 individual assessments of subpopulations (based on baseline characteristics and patient-relevant outcomes planned and reported in the clinical study reports, including protocols) for which results in registry reports are available.
f: Clinical events (benefit outcome): Any event (other than an AE) based on a clinical diagnosis, e.g., nonfatal stroke or nonfatal myocardial infarction, pulmonary embolism.
g: Symptoms (benefit outcome): Any sign of the disease based on the description by the patient, e.g., pain, fatigue.
h: E.g. AEs of special interest in the given indication.

AE: adverse event; AMNOG: Act on the Reform of the Market for Medicinal Products; EPAR: European public assessment report; exp.: expected; HRQoL: health related quality of life; SAE: serious adverse event

Appendix Table 6: Rates of complete information on study methods (by document type and relevant population for approval) - Inclusion of registry reports without results

Information	Complete study information by item and document type Total study population relevant[a] n (%)						Subpopulation relevant[b] n (%)					
	No. of exp. items[c]	AMNOG[d]	EPAR	Publication	Registry report	Non-AMNOG total	No. of exp. items[e]	AMNOG[d]	EPAR	Publication	Registry report	Non-AMNOG total
Study methods (individual items and item categories)												
Randomisation	7	6 (86)	2 (29)	6 (86)	0 (0)	6 (86)	7	6 (86)	3 (43)	7 (100)	0 (0)	7 (100)
Allocation concealment	7	6 (86)	2 (29)	5 (71)	0 (0)	5 (71)	7	6 (86)	3 (43)	6 (86)	0 (0)	6 (86)
Blinding	7	7 (100)	4 (57)	4 (57)	4 (57)	7 (100)	7	7 (100)	4 (57)	5 (71)	7 (100)	7 (100)
Definition of ITT dataset	7	4 (57)	4 (57)	3 (43)	0 (0)	4 (57)	7	5 (71)	4 (57)	7 (100)	3 (43)	7 (100)
No of patients in ITT dataset	7	7 (100)	3 (43)	4 (57)	0 (0)	4 (57)	7	7 (100)	5 (71)	5 (71)	2 (29)	5 (71)
Subtotal risk of bias items	**35**	**30 (86)**	**15 (43)**	**22 (63)**	**4 (11)**	**26 (74)**	**35**	**31 (89)**	**19 (54)**	**30 (86)**	**12 (34)**	**32 (91)**
Intervention[f]	31	31 (100)	25 (81)	24 (77)	23 (74)	30 (97)	32	32 (100)	32 (100)	32 (100)	24 (75)	32 (100)
Comparator[f]	32	32 (100)	20 (63)	23 (72)	20 (63)	29 (91)	32	26 (81)	25 (78)	26 (81)	16 (50)	26 (81)
Methods of outcome measurement	89	70 (79)	28 (31)	31 (35)	5 (6)	38 (43)	71	56 (79)	14 (20)	37 (52)	4 (6)	42 (59)
Study methods total	**187**	**163 (87)**	**88 (47)**	**100 (53)**	**52 (28)**	**123 (66)**	**170**	**145 (85)**	**90 (53)**	**125 (74)**	**56 (33)**	**132 (78)**

a: Original study population investigated in the clinical studies.
b: Subpopulation of the clinical study covering the approved patient population or reflecting the patient population treated with the ACT.
c: Total number (100%) of methods items expected to be reported per document type for the 7 individual assessments of total study populations (items required according to CONSORT) for which no results in registry reports are available.
d: IQWiG dossier assessment and publicly available parts of the company dossier.
e: Total number (100%) of methods items expected to be reported per document type for the 7 individual assessments of subpopulations (items required according to CONSORT) for which no results in registry reports are available.

f: Includes information on dosage, intervals of administration, duration of treatment, route of administration, and concomitant medication.
AMNOG: Act on the Reform of the Market for Medicinal Products; EPAR: European public assessment report; exp.: expected; ITT: intention to treat

Appendix Table 7 Rates of complete information on baseline characteristics and patient-relevant outcomes (by document type and relevant population for approval) – Inclusion of registry reports without results

Information	Complete study information by item and document type											
	Total study population relevant[a] n (%)						Subpopulation relevant[b] n (%)					
	No. of exp. items[c]	AMNOG[d]	EPAR	Publication	Registry report	Non-AMNOG total	No. of exp. items[e]	AMNOG[d]	EPAR	Publication	Registry report	Non-AMNOG total
Study results (individual items and item categories)												
Baseline characteristics												
Age	7	7 (100)	3 (43)	6 (86)	0 (0)	6 (86)	7	4 (57)	2 (29)	4 (57)	0 (0)	4 (57)
Sex	6	6 (100)	2 (33)	5 (83)	0 (0)	5 (83)	7	7 (100)	2 (29)	4 (57)	0 (0)	4 (57)
Severity	5	5 (100)	2 (40)	3 (60)	0 (0)	3 (60)	5	4 (80)	2 (40)	2 (40)	0 (0)	2 (40)
Total baseline characteristics	**18**	**18 (100)**	**7 (39)**	**14 (78)**	**0 (0)**	**14 (78)**	**19**	**15 (79)**	**6 (32)**	**10 (53)**	**0 (0)**	**10 (53)**
Benefit outcomes												
Mortality	7	7 (100)	4 (57)	1 (14)	0 (0)	4 (57)	9	9 (100)	0 (0)	1 (11)	0 (0)	1 (11)
Clinical event[f]	18	18 (100)	0 (0)	4 (22)	0 (0)	4 (22)	13	12 (92)	1 (8)	0 (0)	0 (0)	1 (8)
Symptom[g]	3	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HRQoL	12	4 (33)	0 (0)	0 (0)	0 (0)	0 (0)	4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subtotal benefit outcomes	**40**	**30 (75)**	**4 (10)**	**5 (13)**	**0 (0)**	**8 (20)**	**29**	**21 (72)**	**1 (3)**	**1 (3)**	**0 (0)**	**2 (7)**
Harm outcomes												
AEs	7	7 (100)	1 (14)	2 (29)	0 (0)	3 (43)	7	5 (71)	0 (0)	0 (0)	0 (0)	0 (0)
SAEs	7	7 (100)	0 (0)	2 (29)	0 (0)	2 (29)	7	5 (71)	0 (0)	0 (0)	0 (0)	0 (0)
Withdrawals due to AEs	7	7 (100)	3 (43)	3 (43)	0 (0)	4 (57)	7	5 (71)	0 (0)	0 (0)	0 (0)	0 (0)
Specific AEs[h]	28	27 (96)	7 (25)	12 (43)	0 (0)	13 (46)	21	14 (67)	0 (0)	0 (0)	0 (0)	0 (0)
Subtotal harm outcomes	**49**	**48 (98)**	**11(22)**	**19 (39)**	**0 (0)**	**22 (45)**	**42**	**29 (69)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**

Complete study information by item and document type

Information	Total study population relevant[a] n (%)						Subpopulation relevant[b] n (%)					
	No. of exp. items[c]	AMNOG[d]	EPAR	Publication	Registry report	Non-AMNOG total	No. of exp. items[e]	AMNOG[d]	EPAR	Publication	Registry report	Non-AMNOG total
Total benefit / harm outcomes	**89**	**78 (88)**	**15 (17)**	**24 (27)**	**0 (0)**	**30 (34)**	**71**	**50 (70)**	**1 (1)**	**1(1)**	**0 (0)**	**2 (3)**
Total study results	**107**	**96 (90)**	**22 (21)**	**38 (36)**	**0 (0)**	**44 (41)**	**90**	**65 (72)**	**7 (8)**	**11 (12)**	**0 (0)**	**12 (13)**

a: Original study population investigated in the clinical studies.
b: Subpopulation of the clinical study covering the approved patient population or reflecting the patient population treated with the ACT.
c: Total number (100%) of results items expected to be reported per document type for the 7 individual assessments of total study populations (based on characteristics and patient-relevant outcomes planned and reported in the clinical study reports, including protocols) for which no results in registry reports are available.
d: IQWiG dossier assessment and publicly available parts of the company dossier.
e: Total number (100%) of results items expected to be reported per document type for the 7 individual assessments of subpopulations (based on baseline characteristics and patient-relevant outcomes planned and reported in the clinical study reports, including protocols) for which no results in registry reports are available.
f: Clinical events (benefit outcome): Any event (other than an AE) based on a clinical diagnosis, e.g., nonfatal stroke or nonfatal myocardial infarction, pulmonary embolism.
g: Symptoms (benefit outcome): Any sign of the disease based on the description by the patient, e.g., pain, fatigue.
h: E.g. AEs of special interest in the given indication

AE: adverse event; AMNOG: Act on the Reform of the Market for Medicinal Products; EPAR: European public assessment report; exp.: expected; HRQoL: health related quality of life; SAE: serious adverse event