Gemeinsamer Bundesausschuss

Tezacaftor/ivacaftor

Resolution from: 16. May 2019 Valid until: unlimited
Entry into force on: 16. May 2019
BAnz AT 06 06 2019 B2

Therapeutic indication (based on the marketing authorisation dated 31 October 2018):

Symkevi® is used in conjunction with ivacaftor 150 mg tablets establishing treatment of cystic fibrosis (CF) in patients 12 years and above who display homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and one of the following mutations in the CFTR gene (Cystic Fibrosis Trans-membrane Conductance Regulator): P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

1. Extent of the additional benefit of the medicinal products

Tezacaftor/ivacaftor has been approved as a medicinal product establishing treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan drugs. According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medicinal benefit is considered to be already proven through the grant of marketing authorisation.

In accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure, the Federal Joint Committee (G-BA) determines the extent of the additional benefits for the number of patients and patient groups experiencing additional therapeutically significant benefits. This additional benefit is quantified using the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure.

a) Patients older than 12 years of age in conjunction with cystic fibrosis and who are homozygous for the *F508del* mutation.

Extent of the additional benefit:

Considerable additional benefit

b) Patients older than 12 years of age in conjunction with cystic fibrosis, who are heterozygous for the *F508del* mutation and who display one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

Extent of the additional benefit:

Minor additional benefit

Study results according to endpoints:[1]

a) Patients older than 12 years of age in conjunction with cystic fibrosis and who are homozygous for the *F508del* mutation.

Study VX14-661-106: Tezacaftor/ivacaftor (TEZ/IVA) vs. Placebo

Study VX14-661-106 Endpoint category Endpoint	**TEZ/IVA**	**Placebo**	**TEZ/IVA vs. Placebo**
Mortality			
No deaths occurred.			

Study VX14-661-106 Endpoint category Endpoint	**TEZ/IVA**				**Placebo**				**TEZ/IVA vs. Placebo**
	Baseline		**Absolute change to Week 24**		**Baseline**		**Absolute change to Week 24**		**Mean difference** [a] **[95 % CI]; P value**
	N	**MV (SD)**	**N**	**MV (SD)**	**N**	**MV (SD)**	**N**	**MV (SD)**	***Hedges' g [95% CI]***
Morbidity									
FEV₁									
Absolute change in FEV_1 %[b]	247	59.65 (14.69)	226	3.60 (7.17)	256	60.35 (15.65)	237	-1.47 (6.38)	4.79 [3.58; 6.00]; < 0.0001
Body Mass Index (BMI)									
Absolute change in BMI	248	20.96 (2.95)	237	0.19 (0.82)	256	21.12 (2.88)	245	0.12 (0.70)	0.06 [-0.08; 0.19]; 0.4127
Absolute change in BMI Z-score < 20 years	80	-0.58 (0.95)	76	-0.03 (0.38)	76	-0.37 (0.83)	74	-0.01 (0.31)	-0.04 [-0.15; 0.07]; 0.4713
Symptoms Cystic Fibrosis Questionnaire-Revised (CFQ-R)- Patient Version									
Domain weight problems [c), d)]	225	74.52 (32.47)	214	2.34 (27.59)	232	76.01 (30.77)	218	-1.22 (24.34)	0.51 [-2.89; 3.90]; 0.7695
Gastrointestinal domain [c)]	248	82.03 (16.22)	237	-0.52 (18.30)	256	80.47 (19.07)	244	0.82 (16.48)	-0.10 [-1.93; 1.72]; 0.9109

[1] Data from the dossier evaluation by the G-BA (published on 1 March 2019) unless indicated otherwise.

Study VX14-661-106 Endpoint category Endpoint	TEZ/IVA				Placebo				TEZ/IVA vs. Placebo
	Baseline		Absolute change to Week 24		Baseline		Absolute change to Week 24		Mean difference [a] [95 % CI]; P value
	N	MV (SD)	N	MV (SD)	N	MV (SD)	N	MV (SD)	*Hedges' g [95% CI]*

Study VX14-661-106 Endpoint category Endpoint	TEZ/IVA		Placebo		TEZ/IVA vs. Placebo
	N	Number of patients in conjunction with event n (%)	N	Number of patients in conjunction with event n (%)	Effect estimate [95 % CI]; P value
Morbidity					
Symptoms Cystic Fibrosis Questionnaire-Revised (CFQ-R)- Patient Version					
Domain respiratory system improvement by ≥ 4 points, n (%)	248	121 (48.8)	256	87 (34)	RR [e] 1.44 [1.16; 1.78]; 0.0009
Symptoms pulmonary exacerbations					
Pulmonary exacerbations, n (%)	248	62 (25.0)	256	88 (34.4)	HR [f] 0.64 [0.46; 0.88]; 0.0069
Hospitalisation due to pulmonary exacerbations n (%)	248	22 (8.9)	256	28 (10.9)	HR [f] 0.78 [0.45; 1.37]; 0.3878
i.v. Antibiotics therapy due to pulmonary exacerbations n (%)[2]	248	32 (12.9)	256	54 (21.1)	HR [f] 0.55 [0.36; 0.86]; 0.0080

Study VX14-661-106 Endpoint category Endpoint	TEZ/IVA		Placebo		TEZ/IVA vs. Placebo
	N	Number of PEs (event rate/year)	N	Number of PEs (event rate/year)	Effect estimate [95 % CI]; p value
Morbidity					
Symptoms pulmonary exacerbations					
Number of pulmonary exacerbations (event rate/year)	248	78 (0.64)	256	122 (0.97)	Rate Ratio [g] 0.65 [0.48; 0.88], 0.0054
Number of hospitalisations due to pulmonary	248	26 (0.21)	256	33 (0.26)	Rate Ratio] 0.78 [0.44; 1.36];

[2] Data from the amendment by the G-BA (published on 16 May 2019).

Study VX14-661-106 Endpoint category Endpoint	TEZ/IVA				Placebo				TEZ/IVA vs. Placebo
	Baseline		Absolute change to Week 24		Baseline		Absolute change to Week 24		Mean difference [a] [95 % CI]; P value
	N	MV (SD)	N	MV (SD)	N	MV (SD)	N	MV (SD)	*Hedges' g [95% CI]*
exacerbations (event rate/year)									0.3801
i.v. Antibiotics therapy due to pulmonary exacerbations (event rate/year)[2]	248		39 (0.3)		256		74 (0.6)		Rate Ratio[j] 0.53 [0.34; 0.82]; 0.0042

Study VX14-661-106 Endpoint category Endpoint	TEZ/IVA				Placebo				TEZ/IVA vs. Placebo
	Baseline		Absolute change to Week 24		Baseline		Absolute change to Week 24		Mean difference [a] [95 % CI]; p value
	N	MV (SD)	N	MV (SD)	N	MV (SD)	N	MV (SD)	*Hedges' g [95% CI]*
Quality of life									
Cystic Fibrosis Questionnaire-Revised (CFQ-R) [h] Patient Version									
Domain physical well-being	248	77.56 (20.94)	237	2.01 (16.50)	256	78.23 (21.71)	244	-1.08 (14.78)	3.85 [1.88; 5.82]; 0.0001 *0.31 [0.13; 0.49]*
Domain vitality	225	64.58 (18.59)	214	-0.61 (18.38)	232	62.25 (17.92)	218	-1.22 (15.85)	2.30 [0.10; 4.49]; 0.0401 *0.16 [-0.03; 0.34]*
Domain emotional state	248	82.61 (15.73)	237	-0.02 (12.01)	256	81.90 (16.18)	244	-0.37 (13.61)	0.59 [-1.02; 2.21]; 0.4714
Domain self-perception	248	76.30 (22.09)	237	0.05 (14.80)	256	77.47 (23.15)	244	1.68 (14.70)	-0.51 [-2.31; 1.29]; 0.5773
Domain eating disorders	248	89.74 (17.34)	237	-0.63 (13.64)	256	91.15 (17.06)	244	-0.84 (12.73)	1.05 [-0.59; 2.70]; 0.2094
Domain therapy stress	248	60.53 (19.69)	237	2.88 (13.77)	256	62.11 (20.02)	244	-0.68 (13.03)	3.37 [1.65; 5.10]; 0.0001 *0.31 [0.14;*

Study VX14-661-106 Endpoint category Endpoint	TEZ/IVA				Placebo				TEZ/IVA vs. Placebo
	Baseline		Absolute change to Week 24		Baseline		Absolute change to Week 24		Mean difference [a] [95 % CI]; p value
	N	MV (SD)	N	MV (SD)	N	MV (SD)	N	MV (SD)	*Hedges' g [95% CI]*
									0.49]
Domain subjective health assessment [d]	225	64.35 (21.36)	214	1.82 (15.66)	232	64.89 (20.33)	218	-2.60 (17.35)	3.20 [1.15; 5.24]; 0.0022 *0.24 [0.05; 0.42]*
Domain definition of roles [d]	225	83.93 (17.02)	214	1.73 (14.04)	231	84.02 (16.79)	216	0.31 (14.15)	1.53 [-0.31; 3.37]; 0.1030
Domain social constraints	248	72.06 (16.85)	237	0.82 (12.24)	256	73.93 (16.32)	244	-1.06 (12.21)	1.52 [0.03; 3.01]; 0.0452 *0.16 [-0.01; 0.34]*
SF-12[2]									
Physical Component Summary (PCS)	248	50.9 (6.6)	234	0.8 (5.8)	256	51.9 (6.5)	239	-0.7 (5.7)	1.5 [0.46; 2.54]; 0.005 *0.26 [0.08; 0.44]*
Mental Component Summary (MCS)	248	52.7 (8.0)	234	0.3 (7.8)	256	52.1 (8.0)	239	0.0 (8.2)	0.3 [-1.15;1.75]; 0.6838

Study VX14-661-106 Endpoint category Endpoint	TEZ/IVA		Placebo		TEZ/IVA vs. Placebo
	N	Number of patients in conjunction with event n (%)	N	Number of patients in conjunction with event n (%)	Effect estimate [95 % CI] p value
Side effects					
AEs overall	251	227 (90.4)	258	245 (95.0)	-
SAEs	251	31 (12.4)	258	47 (18.2)	0.68 [0.45; 1.03]; 0.0690 [i]
Serious AEs ((≥ Grade 3)	251	22 (8.8)	258	29 (11.2)	1.28 [0.76; 2.17]; 0.3524 [e]

Discontinuations of therapy due to AEs	251	7 (2.8)	258	8 (3.1)	0.90 [0.33; 2.44]; 0.8353[e)]

Study VX14-661-106	TEZ/IVA		Placebo	
MedDRA System Organ Class Preferred Term with an incidence of ≥ 10% in one of the arms of the study	**N**	**n (%)**	**N**	**n (%)**
Infections and parasitic diseases (SOC)	**251**	**157 (62.5)**	**258**	**175 (67.8)**
Infectious pulmonary exacerbations of CF (PT)	251	75 (29.9)	258	96 (37.2)
Nasopharyngitis (PT)	251	42 (16.7)	258	39 (15.1)
Respiratory, thoracic and mediastinal disorders (SOC)	**251**	**142 (56.6)**	**258**	**159 (61.6)**
Coughing (PT)	251	66 (26.3)	258	84 (32.6)
Increased phlegm (PT)	251	36 (14.3)	258	42 (16.3)
Haemoptysis (PT)	251	26 (10.4)	258	35 (13.6)
Pain in the mouth and pharynx (PT)	251	22 (8.8)	258	29 (11.2)
Gastrointestinal disorders (SOC)	**251**	**83 (33.1)**	**258**	**89 (34.5)**
General disorders and administration site conditions (SOC)	**251**	**60 (23.9)**	**258**	**81 (31.4)**
Pyrexia (PT)	251	28 (11.2)	258	32 (12.4)
Fatigue (PT)	251	16 (6.4)	258	31 (12.0)
Nervous system disorders (SOC)	**251**	**56 (22.3)**	**258**	**48 (18.6)**
Headaches (PT)	251	44 (17.5)	258	37 (14.3)
Investigations (SOC)	**251**	**47 (18.7)**	**258**	**75 (29.1)**
Musculoskeletal and connective tissue disorders (SOC)	**251**	**35 (13.9)**	**258**	**41 (15.9)**
Skin and subcutaneous tissue disorders (SOC)	**251**	**30 (12.0)**	**258**	**36 (14.0)**

a) LS mean difference based on one MMRM: refer to benefit assessment
b) Primary endpoint of the VX14-661-106 Study
c) Scores from 0-100: higher values relate to less symptoms
d) Domain is not contained in the questionnaire version for children
e) Relative risk and p value based on a generalised linear model in conjunction with binomial distribution and logarithmic link function, not adjusted
f) Hazard ratio and p value based on Cox Proportional Hazard Regression
g) Rate ratio and p value based on negative binomial regression model
h) Score from 0-100; higher values relate to a better quality of life
i) Own calculation: refer to benefit assessment

Study VX14-661-106	TEZ/IVA		Placebo	
MedDRA System Organ Class Preferred Term with an incidence of ≥ 10% in one of the arms of the study	**N**	**n (%)**	**N**	**n (%)**
List of abbreviations: BMI: Body Mass Index; CF: Cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FEV_1%: Percent value of the predicted, forced one-second volume; HR: Hazard Ratio; CI: Confidence interval; LS: Least Squares; MedDRA: Medical Dictionary for Regulatory Activities; MMRM: Mixed Model for Repeated Measurement; MV: Median value; MD: Mean difference; n: Number of patients in conjunction with (at least one) event; N: Number of patients assessed; PE: pulmonary exacerbations, PT: Preferred term; RR: relative risk, SD: Standard deviation; SOC: System Organ Class; (S)AE: (serious) adverse event; TEZ/IVA: Tezacaftor/ivacaftor vs.: versus				

Study results according to endpoints:[3]

b) Patients older than 12 years of age in conjunction with cystic fibrosis, who are heterozygous for the *F508del* mutation and who display one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

VX14-661-108 Study: Tezacaftor/ivacaftor (TEZ/IVA) vs. Placebo

Study VX14-661-108 Endpoint category Endpoint	TEZ/IVA	Placebo	TEZ/IVA vs. Placebo
Mortality			
No deaths occurred.			

Study VX14-661-108 Endpoint category Endpoint	TEZ/IVA		Placebo		TEZ/IVA vs. Placebo
	Baseline	**Weeks 4 and 8**	**Baseline**	**Weeks 4 and 8**	**Mean difference** a)

[3] Data from the dossier evaluation by the G-BA (published on 1 March 2019) unless indicated otherwise.

	N	MV (SD)	N	MV (SD)	LS Mean (SE)	N	MV (SD)	N	MV (SD)	LS Mean (SE)	[95 % CI]; p value *Hedges' g [95 % CI]*
Morbidity											
FEV $_1$ [b)]											
Absolute change in FEV_1 %	161	62.1 (14.7)	159	68.5 (15.9)	6.4 (0.5)	161	62.2 (14.3)	160	61.7 (14.1)	-0.3 (0.5)	6.7 [5.5; 7.8], < 0.0001
Body Mass Index (BMI)											
Absolute change in BMI	161	24.1 (4.7)	160	n.c.	0.3 (0.1)	161	24.6 (5.4)	161	n.c.	0.2 (0.1)	0.2 [-0.001; 0.3], 0.0519
Absolute change in BMI Z-score < 20 years Week 8	28	-0.33 (1.42)	28	0.23 (0.44)	-	29	-0.05 (1.35)	28	-0.03 (0.23)	-	-
Symptoms Cystic Fibrosis Questionnaire-Revised (CFQ-R)- Patient Version											
Domain weight problems [c), d)]	155	87.1 (24.7)	155	91.3 (17.1)	4.1 (1.2)	156	87.8 (21.8)	155	88.1 (21.7)	0.5 (1.2)	3.6 [0.4; 6.7], 0.0265 *0.2 [0.0; 0.5]*
Gastrointestinal domain [c)]	161	84.2 (16.5)	161	83.6 (17.4)	-0.6 (0.9)	161	83.6 (17.1)	160	85.8 (15.2)	1.9 (0.9)	-2.6 [-4.8; -0.4], 0.0227 *-0.2 [-0.5; -0.02]*

Study VX14-661-108 Endpoint category Endpoint	**TEZ/IVA**		**Placebo**		**TEZ/IVA vs. Placebo**
	N	**Number of patients in conjunction with event n (%)**	**N**	**Number of patients in conjunction with event n (%)**	**Effect estimate [95 % CI]; p value**
Morbidity					
Symptoms Cystic Fibrosis Questionnaire-Revised (CFQ-R)- Patient Version					
Domain respiratory system improvement by ≥ 4 points, n (%)	161	111 (68.9)	161	56 (34.8)	RR [e)] 1.9 [1.5; 2.4]; < 0.0001
Symptoms pulmonary exacerbations					
Pulmonary exacerbations, n (%)	161	11 (6.8)	161	19 (11.8)	HR [f)] 0.5 [0.3; 1.2]; 0.1096
Hospitalisation due to	161	3 (1.9)	161	5 (3.1)	HR [f)] 0.6 [0.1; 2.4];

Study VX14-661-108 Endpoint category Endpoint	TEZ/IVA					Placebo					TEZ/IVA vs. Placebo
	Baseline		Weeks 4 and 8			Baseline		Weeks 4 and 8			Mean difference [a] [95 % CI]; p value *Hedges' g [95 % CI]*
	N	MV (SD)	N	MV (SD)	LS Mean (SE)	N	MV (SD)	N	MV (SD)	LS Mean (SE)	
pulmonary exacerbations n (%)											0.4547
i.v. Antibiotic therapy due to pulmonary exacerbations n (%)[4]	161		4 (2.5)			161		9 (5.6)			HR [f] 0.41 [0.12; 1.33]; 0.1379

Study VX14-661-108 Endpoint category Endpoint	TEZ/IVA					Placebo					TEZ/IVA vs. Placebo
	Baseline		Weeks 4 and 8			Baseline		Weeks 4 and 8			Mean difference [a] [95 % CI]; P value *Hedges' g [95 % CI]*
	N	MV (SD)	N	MV (SD)	LS Mean (SE)	N	MV (SD)	N	MV (SD)	LS Mean (SE)	
Quality of life											
Cystic Fibrosis Questionnaire-Revised (CFQ-R) [g]- Patient Version											
Domain physical well-being	161	73.3 (22.3)	161	76.7 (21.7)	3.8 (1.1)	161	70.2 (23.0)	160	67.6 (24.6)	-2.9 (1.1)	6.8 [4.0; 9.5]; < 0.0001 *0.5 [0.3; 0.7]*
Domain vitality [d]	155	60.5 (17.7)	155	65.4 (17.6)	5.4 (1.1)	156	59.2 (19.9)	155	57.0 (19.9)	-2.5 (1.1)	7.9 [5.2; 10.5], < 0.0001 *0.6 [0.3; 0.8*]
Domain emotional state	161	82.0 (15.8)	161	83.5 (15.0)	1.8 (0.7)	161	80.2 (15.9)	160	79.6 (15.7)	-0.8 (0.7)	2.5 [0.8; 4.2], 0.0036 *0.3 [0.1; 0.5*]
Domain self-perception	161	82.9 (17.3)	161	85.8 (16.5)	2.1 (0.8)	161	84.1 (18.0)	161	84.0 (17.6)	-0.03 (0.8)	2.2 [0.5; 3.9], 0.0123 *0.2 [0.0; 0.4]*
Domain eating disorders	161	93.0 (14.5)	161	92.4 (14.2)	-0.8 (0.8)	161	93.4 (12.9)	160	91.1 (14.6)	-2.2 (0.8)	1.4 [-0.5; 3.4], 0.1560

[4] Data from the amendment by the G-BA (published on 16 May 2019)

Study VX14-661-108 Endpoint category Endpoint	TEZ/IVA					Placebo					TEZ/IVA vs. Placebo
	Baseline		Weeks 4 and 8			Baseline		Weeks 4 and 8			Mean difference [a] [95 % CI]; p value *Hedges' g [95 % CI]*
	N	MV (SD)	N	MV (SD)	LS Mean (SE)	N	MV (SD)	N	MV (SD)	LS Mean (SE)	
Domain therapy stress	161	64.0 (21.8)	161	67.0 (21.8)	2.5 (0.9)	161	62.7 (21.8)	161	62.2 (22.2)	-0.3 (0.9)	2.9 [0.9; 4.9], 0.0056 *0.2 [0.0; 0.5]*
Domain subjective health assessment [d]	155	65.9 (20.6)	155	71.3 (19.1)	6.1 (1.0)	156	63.9 (21.4)	156	61.4 (21.0)	-2.8 (1.0)	8.9 [6.7; 11.2], <0.0001 *0.7 [0.5; 1.0]*
Domain definition of roles [d]	155	83.9 (16.6)	155	84.5 (17.2)	0.7 (1.0)	156	83.0 (16.2)	155	80.3 (17.9)	-2.5 (1.0)	3.1 [0.8; 5.5], 0.0086 *0.3 [0.0; 0.5]*
Domain social constraints	161	69.9 (17.7)	161	73.0 (16.7)	3.1 (0.8)	161	67.4 (18.3)	161	67.7 (18.1)	0.3 (0.8)	2.8 [1.0; 4.6], 0.0021 *0.3 [0.1; 0.5]*
SF-12											
Physical Component Summary (PCS)	160	50.0 (7.8)	160	n.c.	1.4 (0.4)	159	49.6 (7.2)	158	n.c.	-1.0 (0.4)	2.4 [1.5; 3.3], < 0.0001 *0.5 [0.3; 0.7]*
Mental Component Summary (MCS)	160	52.6 (7.1)	160	n.c.	0.7 (0.4)	159	51.6 (9.0)	158	n.c.	-0.7 (0.4)	1.3 [0.3; 2.4], 0.0113 *0.2 [0.0; 0.5]*

Study VX14-661-108 Endpoint category Endpoint	TEZ/IVA		Placebo		TEZ/IVA vs. Placebo
	N	Patients in conjunction with event n (%)	N	Patients in conjunction with event n (%)	RR [95 % CI]; p value
Side effects					
AEs overall	162	117 (72.2)	162	126 (77.8)	-
SAEs	162	8 (4.9)	162	14 (8.6)	0.6 [0.2; 1.3]; 0.1889 [h]
Serious AEs ((≥ Grade 3)	162	4 (2.5)	162	9 (5.6)	0.4 [0.1; 1.4]; 0.1571 [e]

Study VX14-661-108 Endpoint category Endpoint	TEZ/IVA		Placebo		TEZ/IVA vs. Placebo
	N	Patients in conjunction with event n (%)	N	Patients in conjunction with event n (%)	RR [95 % CI]; p value
Discontinuations of therapy due to AEs	162	0	162	1 (0.6)	0.0 [0.0; -]; 0.9843 e)

Study VX14-661-108	TEZ/IVA		Placebo		TEZ/IVA vs. Placebo
MedDRA System Organ Class Preferred Term with an incidence of ≥ 10% in one of the arms of the study	N	n (%)	N	n (%)	RR [95% CI]; p-value
Respiratory, thoracic and mediastinal disorders (SOC)	**162**	**58 (35.8)**	**162**	**73 (45.1)**	**0.8 [0.6; 0.997]; 0.0471 e)**
Coughing (PT)	162	23 (14.2)	162	30 (18.5)	n.c.
Infections and parasitic diseases (SOC)	**162**	**57 (35.2)**	**162**	**63 (38.9)**	**0.9 [0.7; 1.2], 0.6218 e)**
Infectious pulmonary exacerbations of CF (PT)	162	21 (13.0)	162	31 (19.1)	n.c.
Gastrointestinal disorders (SOC)	**162**	**37 (22.8)**	**162**	**32 (19.8)**	**1.1 [0.7; 1.7], 0.5690 e)**
Nervous system disorders (SOC)	**162**	**30 (18.5)**	**162**	**19 (11.7)**	**1.5 [0.9; 2.6], 0.1013 e)**
Headaches (PT)	162	19 (11.7)	162	13 (8.0)	n.c.
General disorders and administration site conditions (SOC)	**162**	**26 (16.0)**	**162**	**32 (19.8)**	**0.8 [0.5; 1.3]; 0.3449 e)**
Investigations (SOC)	**162**	**17 (10.5)**	**162**	**28 (17.3)**	**0.6 [0.3; 1.1]; 0.0772 h)**

a) LS mean difference based on a mixed effects model: refer to benefit assessment
b) Primary endpoint of the VX14-661-108 Study
c) Scores from 0-100: higher values relate to less symptoms
d) Domain is not contained in the questionnaire version for children
e) Relative risk and p value based on a generalised linear model in conjunction with binomial distribution
f) Hazard ratio and p value based on Cox Proportional Hazard Regression
g) Score from 0-100; higher values relate to a better quality of life
h) Own calculation: refer to benefit assessment

List of abbreviations:

BMI: Body Mass Index; CF: Cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FEV_1%: Percent value of the predicted, forced one-second volume; HR: Hazard ratio; CI: Confidence interval; LS: Least Squares; MedDRA: Medical Dictionary for Regulatory Activities; MD: Mean difference; n: Number of patients in conjunction with (at least one) event; N: Number of patients assessed; n.c: not calculable; PE: pulmonary exacerbations, PT: Preferred term; RR: relative risk, SD: Standard deviation; SE: Standard error; SF-12:

Study VX14-661-108	TEZ/IVA		Placebo		TEZ/IVA vs. Placebo
MedDRA System Organ Class Preferred Term with an incidence of ≥ 10% in one of the arms of the study	**N**	**n (%)**	**N**	**n (%)**	**RR [95% CI]; p-value**
Short Form 12; SOC: System Organ Class; (S)AE: (serious) adverse event; TEZ/IVA: Tezacaftor/ivacaftor vs.: versus					

2. Number of patients or demarcation of patient groups eligible for treatment

a) Patients older than 12 years of age in conjunction with cystic fibrosis and who are homozygous for the *F508del* mutation.

Approx. 2400 patients

b) Patients older than 12 years of age in conjunction with cystic fibrosis, who are heterozygous for the *F508del* mutation and who display one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

Approx. 200-300 patients

3. Requirements for quality-assured treatment

The requirements of the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information for Symkevi® (active ingredient: Tezacaftor/ivacaftor established under the following link (last access: 4. April 2019):

https://www.ema.europa.eu/documents/product-information/symkevi-epar-product-information_de.pdf

The introduction and monitoring of treatment in conjunction with Tezacaftor/ivacaftor may only be implemented by experienced physicians in therapy with patients with cystic fibrosis.

4. Treatment costs

Annual treatment costs:

a) Patients older than 12 years of age in conjunction with cystic fibrosis and who are homozygous for the *F508del-* mutation.

Designation of the therapy	Annual treatment costs/patient
Tezacaftor/ivacaftor	€ 82,844.70
Ivacaftor	€ 131,123.25
Overall:	€ 213,967.95

Expenses after deduction of statutory discounts (status: Lauer-Taxe: 15. April 2019)

Expenses for additionally required SHI services: omitted

b) Patients older than 12 years of age in conjunction with cystic fibrosis, who are heterozygous for the *F508del* mutation and who display one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

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