

# Resolution



Gemeinsamer  
Bundesausschuss

## of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Appendix XII – Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V – Tezacaftor/ivacaftor

From 16. May 2019

At its meeting on 16. May 2019, the Federal Joint Committee (G-BA) decided to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive) in the version dated 18 December 2008/22 January 2009 (BAnz. No. 49a dated 31 March 2009), last amended on TT. Monat JJJJ (BAnz. AT TT.MM.JJJJ BX), to be amended as follows:

- I. **Appendix XII will be amended as follows in alphabetical order to include the active ingredient Tezacaftor/ivacaftor (cystic fibrosis with homozygous *F508del* mutation or heterozygous *F508del* mutation and a further mutation in the CFTR gene):**

## Tezacaftor/ivacaftor

Resolution from: 16. May 2019  
Effective as of: 16. May 2019  
BAz AT TT. MM JJJJ Bx

### 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:<sup>1</sup>

- 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
<b>Mortality</b>					
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 <sup>a)</sup> [95 % CI]; P value
	N	MV (SD)	N	MV (SD)	N	MV (SD)	N	MV (SD)	Hedges' g [95% CI]
<b>Morbidity</b>									
<b>FEV<sub>1</sub></b>									
Absolute change in FEV <sub>1</sub> % <sup>b)</sup>	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
<b>Body Mass Index (BMI)</b>									
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
<b>Symptoms Cystic Fibrosis Questionnaire-Revised (CFQ-R)- Patient Version</b>									
Domain weight problems <sup>c), d)</sup>	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
Gastrointesti nal domain <sup>c)</sup>	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

<sup>1</sup> 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
	N	Number of patients in conjunction with event n (%)	N	Number of patients in conjunction with event n (%)	Effect estimate [95 % CI]; P value
<b>Morbidity</b>					
<b>Symptoms Cystic Fibrosis Questionnaire-Revised (CFQ-R)- Patient Version</b>					
Domain respiratory system improvement by ≥ 4 points, n (%)	248	121 (48.8)	256	87 (34)	RR <sup>e)</sup> 1.44 [1.16; 1.78]; 0.0009
<b>Symptoms pulmonary exacerbations</b>					
Pulmonary exacerbations, n (%)	248	62 (25.0)	256	88 (34.4)	HR <sup>f)</sup> 0.64 [0.46; 0.88]; 0.0069
Hospitalisation due to pulmonary exacerbations n (%)	248	22 (8.9)	256	28 (10.9)	HR <sup>f)</sup> 0.78 [0.45; 1.37]; 0.3878
i.v. Antibiotics therapy due to pulmonary exacerbations n (%) <sup>2</sup>	248	32 (12.9)	256	54 (21.1)	HR <sup>f)</sup> 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
<b>Morbidity</b>					
<b>Symptoms pulmonary exacerbations</b>					
Number of pulmonary exacerbations (event rate/year)	248	78 (0.64)	256	122 (0.97)	Rate Ratio <sup>g)</sup> 0.65 [0.48; 0.88], 0.0054
Number of hospitalisations due to pulmonary exacerbations (event rate/year)	248	26 (0.21)	256	33 (0.26)	Rate Ratio <sup>g)</sup> 0.78 [0.44; 1.36]; 0.3801
i.v. Antibiotics therapy due to pulmonary exacerbations (event rate/year) <sup>2</sup>	248	39 (0.3)	256	74 (0.6)	Rate Ratio <sup>g)</sup> 0.53 [0.34; 0.82]; 0.0042

<sup>2</sup> 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 <sup>a)</sup> [95 % CI]; p value
	N	MV (SD)	N	MV (SD)	N	MV (SD)	N	MV (SD)	Hedges' g [95% CI]
<b>Quality of life</b>									
<b><i>Cystic Fibrosis Questionnaire-Revised (CFQ-R) <sup>h)</sup> Patient Version</i></b>									
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; 0.49]
Domain subjective health assessment <sup>d)</sup>	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 <sup>d)</sup>	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]
<b>SF-12<sup>2</sup></b>									
Physical Component	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];

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 <sup>a)</sup> [95 % CI]; p value
	N	MV (SD)	N	MV (SD)	N	MV (SD)	N	MV (SD)	Hedges' g [95% CI]
Summary (PCS)									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
<b>Side effects</b>					
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 <sup>i)</sup>
Serious AEs ( $\geq$ Grade 3)	251	22 (8.8)	258	29 (11.2)	1.28 [0.76; 2.17]; 0.3524 <sup>e)</sup>
Discontinuations of therapy due to AEs	251	7 (2.8)	258	8 (3.1)	0.90 [0.33; 2.44]; 0.8353 <sup>e)</sup>

Study VX14-661-106	TEZ/IVA		Placebo	
MedDRA System Organ Class	N	n (%)	N	n (%)
Preferred Term with an incidence of $\geq$ 10% in one of the arms of the study				
<b>Infections and parasitic diseases (SOC)</b>	<b>251</b>	<b>157 (62.5)</b>	<b>258</b>	<b>175 (67.8)</b>
Infectious pulmonary exacerbations of CF (PT)	251	75 (29.9)	258	96 (37.2)
Nasopharyngitis (PT)	251	42 (16.7)	258	39 (15.1)
<b>Respiratory, thoracic and mediastinal disorders (SOC)</b>	<b>251</b>	<b>142 (56.6)</b>	<b>258</b>	<b>159 (61.6)</b>
Coughing (PT)	251	66 (26.3)	258	84 (32.6)

Study VX14-661-106	TEZ/IVA		Placebo	
MedDRA System Organ Class Preferred Term with an incidence of $\geq 10\%$ in one of the arms of the study	N	n (%)	N	n (%)
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)
<b>Gastrointestinal disorders (SOC)</b>	<b>251</b>	<b>83 (33.1)</b>	<b>258</b>	<b>89 (34.5)</b>
<b>General disorders and administration site conditions (SOC)</b>	<b>251</b>	<b>60 (23.9)</b>	<b>258</b>	<b>81 (31.4)</b>
Pyrexia (PT)	251	28 (11.2)	258	32 (12.4)
Fatigue (PT)	251	16 (6.4)	258	31 (12.0)
<b>Nervous system disorders (SOC)</b>	<b>251</b>	<b>56 (22.3)</b>	<b>258</b>	<b>48 (18.6)</b>
Headaches (PT)	251	44 (17.5)	258	37 (14.3)
<b>Investigations (SOC)</b>	<b>251</b>	<b>47 (18.7)</b>	<b>258</b>	<b>75 (29.1)</b>
<b>Musculoskeletal and connective tissue disorders (SOC)</b>	<b>251</b>	<b>35 (13.9)</b>	<b>258</b>	<b>41 (15.9)</b>
<b>Skin and subcutaneous tissue disorders (SOC)</b>	<b>251</b>	<b>30 (12.0)</b>	<b>258</b>	<b>36 (14.0)</b>
<p>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</p> <p>List of abbreviations:  BMI: Body Mass Index; CF: Cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FEV<sub>1</sub>%; 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</p>				

### Study results according to endpoints:<sup>3</sup>

- 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
<b>Mortality</b>											
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 <sup>a)</sup> [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)	
<b>Morbidity</b>											
<b>FEV<sub>1</sub><sup>b)</sup></b>											
Absolute change in FEV <sub>1</sub> %	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
<b>Body Mass Index (BMI)</b>											
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)	-	-

<sup>3</sup> Data from the dossier evaluation by the G-BA (published on 1 March 2019) unless indicated otherwise.



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 <sup>a)</sup> [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)	
<b>Symptoms Cystic Fibrosis Questionnaire-Revised (CFQ-R)- Patient Version</b>											
Domain weight problems <sup>c)</sup> , <sup>d)</sup>	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 <sup>c)</sup>	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
<b>Morbidity</b>											
<b>Symptoms Cystic Fibrosis Questionnaire-Revised (CFQ-R)- Patient Version</b>											
Domain respiratory system improvement by ≥ 4 points, n (%)	161	111 (68.9)				161	56 (34.8)				RR <sup>e)</sup> 1.9 [1.5; 2.4]; < 0.0001
<b>Symptoms pulmonary exacerbations</b>											
Pulmonary exacerbations, n (%)	161	11 (6.8)				161	19 (11.8)				HR <sup>f)</sup> 0.5 [0.3; 1.2]; 0.1096
Hospitalisation due to pulmonary exacerbations n (%)	161	3 (1.9)				161	5 (3.1)				HR <sup>f)</sup> 0.6 [0.1; 2.4]; 0.4547
i.v. Antibiotic therapy due to pulmonary exacerbations n (%) <sup>4</sup>	161	4 (2.5)				161	9 (5.6)				HR <sup>f)</sup> 0.41 [0.12; 1.33]; 0.1379

<sup>4</sup> 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 <sup>a)</sup>
	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]
<b>Quality of life</b>											
<b>Cystic Fibrosis Questionnaire-Revised (CFQ-R)<sup>9)</sup>- Patient Version</b>											
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 <sup>d)</sup>	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
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 <sup>d)</sup>	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 <sup>d)</sup>	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]
<b>SF-12</b>											
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]

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 <sup>a)</sup> [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)	
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
<b>Side effects</b>					
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 <sup>h)</sup>
Serious AEs ( $\geq$ Grade 3)	162	4 (2.5)	162	9 (5.6)	0.4 [0.1; 1.4]; 0.1571 <sup>e)</sup>
Discontinuations of therapy due to AEs	162	0	162	1 (0.6)	0.0 [0.0; -]; 0.9843 <sup>e)</sup>

Study VX14-661-108	TEZ/IVA		Placebo		TEZ/IVA vs. Placebo
MedDRA System Organ Class Preferred Term with an incidence of $\geq$ 10% in one of the arms of the study	N	n (%)	N	n (%)	RR [95% CI]; p- value
<b>Respiratory, thoracic and mediastinal disorders (SOC)</b>	162	58 (35.8)	162	73 (45.1)	0.8 [0.6; 0.997]; 0.0471 <sup>e)</sup>
Coughing (PT)	162	23 (14.2)	162	30 (18.5)	n.c.
<b>Infections and parasitic diseases (SOC)</b>	162	57 (35.2)	162	63 (38.9)	0.9 [0.7; 1.2], 0.6218 <sup>e)</sup>
Infectious pulmonary exacerbations of CF (PT)	162	21 (13.0)	162	31 (19.1)	n.c.
<b>Gastrointestinal disorders (SOC)</b>	162	37 (22.8)	162	32 (19.8)	1.1 [0.7; 1.7], 0.5690 <sup>e)</sup>

Study VX14-661-108	TEZ/IVA		Placebo		TEZ/IVA vs. Placebo
MedDRA System Organ Class Preferred Term with an incidence of $\geq 10\%$ in one of the arms of the study	N	n (%)	N	n (%)	RR [95% CI]; p-value
<b>Nervous system disorders (SOC)</b>	162	30 (18.5)	162	19 (11.7)	1.5 [0.9; 2.6], 0.1013 <sup>e)</sup>
Headaches (PT)	162	19 (11.7)	162	13 (8.0)	n.c.
<b>General disorders and administration site conditions (SOC)</b>	162	26 (16.0)	162	32 (19.8)	0.8 [0.5; 1.3]; 0.3449 <sup>e)</sup>
<b>Investigations (SOC)</b>	162	17 (10.5)	162	28 (17.3)	0.6 [0.3; 1.1]; 0.0772 <sup>h)</sup>
<p>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</p> <p>List of abbreviations:  BMI: Body Mass Index; CF: Cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FEV<sub>1</sub>%; 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: Short Form 12; SOC: System Organ Class; (S)AE: (serious) adverse event; TEZ/IVA: Tezacaftor/ivacaftor vs.: versus</p>					

## 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](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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Overall:	€ 213,967.95

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

Expenses for additionally required SHI services: omitted

**II. The resolution will enter into force on the Internet on the websites of the Federal Joint Committee on the day of its publication on 16. May 2019 .**

The justification to this resolution is published on the website of the Federal Joint Committee at [www.g-ba.de](http://www.g-ba.de) .

Berlin, 16. May 2019

Federal Joint Committee  
in accordance with Section 91 SGB V  
Chair

Prof. Hecken