Gemeinsamer Bundesausschuss

Ivacaftor (Exceeding the € 50 Million Limit: Cystic Fibrosis, Patients from 6 Years of Age with G551D Mutation)

Resolution of: 20 February 2020 Valid until: unlimited
Entry into force on: 20 February 2020
Federal Gazette, BAnz AT 19 06 2020 B3

Therapeutic indication (according to the product information of April 2019):

"Kalydeco tablets are indicated for the treatment of adults, adolescents, and children aged 6 years and older and weighing 25 kg or more with cystic fibrosis (CF) who have one of the following gating (class III) mutations in the *CFTR* gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R (see Sections 4.4 and 5.1)."

The present resolution relates exclusively to the therapeutic indication of cystic fibrosis in patients aged 6 years and older *with a body weight of at least 25 kg bearing the gating mutation G551D in the CFTR gene.*

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

a) Patients aged 6 to 11 years with cystic fibrosis with a G551D mutation in the *CFTR* gene

Appropriate comparator therapy:

- Best supportive care.

Best supportive care (BSC) is defined as the therapy that ensures the best possible, patient-individual optimised, supportive treatment to alleviate symptoms and improve the quality of life (especially antibiotics for pulmonary infections, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy (in the sense of the HeilmittelRichtlinie (Remedies Directive)), making full use of all possible dietary measures).

Extent and probability of the additional benefit of ivacaftor compared with best supportive care:

Hint for a non-quantifiable additional benefit.

a) Patients aged 12 years and older with cystic fibrosis with a G551D mutation in the *CFTR* gene

- Best supportive care.

Best supportive care (BSC) is defined as the therapy that ensures the best possible, patient-individual optimised, supportive treatment to alleviate symptoms and improve the quality of life (especially antibiotics for pulmonary infections, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy (in the sense of the HeilmittelRichtlinie (Remedies Directive)), making full use of all possible dietary measures).

Extent and probability of the additional benefit of ivacaftor compared with best supportive care:

Hint for a considerable additional benefit.

Study results according to endpoints:[1]

a) Patients aged 6 to 11 years with cystic fibrosis with a G551D mutation in the *CFTR* gene

Study VX08-770-103: Ivacaftor + BSC vs placebo + BSC

Endpoint category Endpoint	Ivacaftor + BSC		Placebo + BSC		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Mortality					
No deaths occurred					

Endpoint category Endpoint	Ivacaftor + BSC		Placebo + BSC		Group difference
	N	Number of events n_E (n_E/patient years)[a]	N	Number of events n_E (n_E/patient years)[a]	Rate ratio [95% CI]; p value
Morbidity					
Pulmonary exacerbations	20	4 (0.22[b])	18	3 (0.21[b])	no data available
Hospitalisations because of pulmonary exacerbations	20	2 (0.11[b])	18	1 (0.07[b])	no data available
Endpoint category Endpoint	**Ivacaftor + BSC**		**Placebo + BSC**		**Group difference**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p value**
Morbidity					
Pulmonary exacerbations	20	4 (20.0)	18	3 (16.7)	1.20 [0.31; 4.65]; 0.847[c]
Hospitalisations because of pulmonary exacerbations	20	2 (10.0)	18	1 (5.6)	1.80 [0.18; 18.21]; 0.712[c]

a: Event rate (n_E/patient years) is calculated by dividing the total number of events by the total number of years (sum of time in the study of all patients included in the analysis)
b: Calculation of the IQWiG
c: RR and CI Calculation of the IQWiG. p value own calculation, unconditional exact test (CSZ method)
BSC: best supportive care; CI: confidence interval; n: number of patients with (at least 1) event; N: number of patients with at least one dose of the study medication; n_E: number of events; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event.

[1] Data from the dossier evaluation of the IQWiG (A19-65) unless otherwise indicated.

Study VX08-770-103: Ivacaftor + BSC vs placebo + BSC

Endpoint category Endpoint	Ivacaftor + BSC			Placebo + BSC			Group difference
	N[a]	Values at start of study MV (SD)	Change at the end of study[b] MV (SD)	N[a]	Values at start of study MV (SD)	Change at the end of study[b] MV (SD)	MD [95% CI]; p value[c]
Morbidity							
FEV_1[i]							
FEV_1 (absolute change) %[d]	20	85.03 (12.86)	10.93 (14.77)	14[e]	83.42 (19.61)	1.38 (9.51)	10.21 [2.28; 18.14]; 0.013[f]
FEV_1 (relative change) %[d]	20	85.03 (12.86)	14.67 (19.69)	14[e]	83.42 (19.61)	2.46 (12.34)	13.72 [3.69, 23.74]; 0.009[f]
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[d]							
CFQ-R, domains on symptomatology[d]							
Respiratory system	20	80.00 (17.61)	6.25 (19.10)	17	82.87 (14.98)	2.97 (16.54)	5.42 [−2.98; 13.82]; 0.198
Gastrointestinal symptoms	20	76.67 (26.72)	10.00 (24.42)	16	72.24 (20.61)	11.90 (28.05)	5.55 [−4.83; 15.93]; 0.284
Weight problems	Domain not included in questionnaire for children 6 to 11 years						
CFQ-R, domains on symptomatology[d] – parent/caretaker version additionally shown							
Respiratory system	20	81.38 (15.75)	5.28 (17.14)	17	81.48 (16.50)	0.39 (14.36)	3.83 [−2.17; 9.83]; 0.203
Gastrointestinal symptoms	20	79.46 (14.98)	4.44 (14.13)	16	77.79 (17.04)	2.38 (10.82)	1.23 [−3.29; 5.74]; 0.584
Weight problems	20	81.68 (25.30)	14.99 (31.48)	16	66.67 (28.02)	7.14 (23.29)	13.14 [2.13; 24.14]; 0.021 Hedges' g: 0.86 [0.17; 1.56]
Health status							
EQ5D-VAS[d]	Endpoint not recorded						
BMI[j] ([kg/m²] absolute change)	20	17.64 (2.77)	1.46 (0.94)	14[e]	17.51 (1.62)	0.36 (0.81)	1.00 [0.36; 1.64]; 0.003[f]
BMI[j] (age dependent z-score, absolute change)	20	0.19 (0.99)	0.30 (0.29)	14[e]	0.23 (0.85)	−0.10 (0.28)	0.39 [0.19; 0.58], < 0.001[f]
Sweat chloride concentration (additionally shown) [k]							
Absolute change at Week 48[mmol/l]	24[l]	104.31 (14.54)	-59.00 (17.78)	24[l]	104.79 (8.87)	−4.90 (9.12)	-54.54 [-63.10; -45.97]; < 0.001
Health-related quality of life							
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[d]							
CFQ-R, domains on health-related quality of life							
Physical well-being	20	86.21 (17.65)	2.79 (11.22)	16	87.96 (15.74)	3.58 (12.06)	−1.11 [−7.25; 5.02]; 0.714

Study VX08-770-103: Ivacaftor + BSC vs placebo + BSC

Endpoint category Endpoint	Ivacaftor + BSC			Placebo + BSC			Group difference
	N[a]	Values at start of study MV (SD)	Change at the end of study[b] MV (SD)	N[a]	Values at start of study MV (SD)	Change at the end of study[b] MV (SD)	MD [95% CI]; p value[c]
Health-related quality of life							
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[d]							
CFQ-R, domains on health-related quality of life							
Emotional state	20	77.09 (16.52)	7.50 (10.96)	16	81.24 (13.87)	5.96 (15.66)	1.31 [−2.21; 4.83]; 0.455
Vitality	Domain not included in questionnaire for children 6 to 11 years						
Social limitations	20	68.82 (18.24)	5.48 (12.20)	16	72.67 (20.96)	0.79 (19.15)	3.10 [−2.12; 8.32]; 0.235
Role function	Domain not included in questionnaire for children 6 to 11 years						
Body image	20	88.34 (19.58)	6.66 (12.16)	16	92.60 (12.04)	0.79 (8.10)	2.71 [−2.00; 7.43]; 0.250
Eating disorders	20	82.23 (22.34)	13.33 (23.80)	16	85.81 (20.09)	6.34 (17.80)	1.91 [−4.67; 8.48]; 0.559
Burden of therapy	20	73.35 (23.75)	0.56 (19.55)	16	68.52 (27.03)	5.56 (21.68)	−0.96 [−8.97; 7.05]; 0.809
Subjective health assessment	Domain not included in questionnaire for children 6 to 11 years						
CFQ-R, domains on health-related quality of life – parent/caretaker version additionally shown							
Physical well-being	20	83.53 (20.80)	4.39 (1.00)	16	93.01 (15.03)	−0.79 (11.16)	−0.087 [−5.62; 5.45); 0.975
Emotional state	20	86.67 (14.18)	0.01 (11.45)	16	84.46 (14.81)	0.49 (8.86)	−1.51 [−6.26; 3.23]; 0.519
Vitality	20	72.00 (16.69)	5.67 (13.56)	16	77.40 (18.60)	6.68 (15.91)	1.70 [−5.29; 8.68]; 0.624
Body image	20	85.01 (24.52)	10.00 (22.19)	16	87.66 (18.23)	0 (18.47)	3.14 [−3.26; 9.54]; 0.324
Eating disorders	20	85.00 (22.23)	8.34 (26.21)	16	76.84 (25.66)	5.96 (16.79)	−1.81 [−10.67; 7.05]; 0.680
Burden of therapy	20	64.46 (17.53)	−0.56 (17.45)	16	59.88 (26.45)	−2.38 (26.90)	2.40 [−7.17; 11.98]; 0.613
Subjective perception of health	20	77.80 (16.91)	6.11 (12.72)	16	80.26 (21.41)	−0.79 (19.21)	−0.13 [−7.67; 7.41]; 0.973
Problems at school	20	76.12 (21.42)	6.11 (17.45)	16	78.41 (18.85)	−3.17 (24.79)	2.66 [−6.65; 11.97]; 0.565

a: Number of patients considered in MMRM to calculate the effect estimate; the values at the start of study may be based on more patients and the values at the end of study on fewer patients.
b: Refers to the change from the start of study at the last time of measurement
c: MMRM; effect represents the difference between the treatment groups in the changes averaged over the course of the study between the respective measurement time and the start of study. Model: dependent variable absolute change (or relative change for "FEV_1, relative change") from baseline; time of study and treatment as fixed effects; adjusted for continuous baseline values age, FEV_1 (as % of standardised normal value), and – for CFQ-R domains – CFQ-R domain score.
d: For FEV_1 as % of the standardised normal value; higher values mean a better function, health-related quality of life or symptomatology; a positive group difference corresponds to an advantage

for ivacaftor.
e: According to the study report, all but one patient on the placebo arm were included in the evaluation of the total population (over the entire study period). The statement of the pharmaceutical company regarding the evaluation of the sub-population – i.e. that 4 of 18 patients are missing in the placebo arm – is therefore implausible. An N of 17 is assumed.
f: MMRM; effect represents the difference between the treatment groups of the changes from the start of study at week 48. Model: dependent variable: absolute change from baseline; treatment×time of study, time of study, and treatment as fixed effects; adjusted for continuous baseline values of age (for FEV_1, only in Study VX08-770-102), EQ-5D VAS score and FEV_1 (as % of standardised normal value), and sweat chloride concentration. Further adjustment according to continuous baseline values: At BMI (z-score) according to BMI (z-score).
g: Linear mixed mode; effect represents the difference between the treatment groups of the changes from the start of study at week 48. Model: dependent variable absolute change from baseline; treatment as fixed effect, treatment×time of study, time of study, treatment and intercept as random effects; adjusted for baseline values of age group and FEV_1 category (as % of standardised normal value).
h: Based on participants at the age of ≤ 20 years N = 24 (ivacaftor + BSC) vs N = 23 (placebo + BSC)
i: Primary endpoint of the Studies VX08-770-102 and VX08-770-103
j: Absolute change
k: Data from the dossier of the pharmaceutical company.
l: Values at the start of study. The values at the end of study may be based on fewer patients; relative to the total population, including patients with a body weight < 25 kg.

BMI: Body Mass Index; BSC: best supportive care; BMI: Body Mass Index; CFQ-R: Cystic Fibrosis Questionnaire-Revised; EQ-5D: European Quality of Life Questionnaire 5 Dimensions; FEV_1: forced expiratory volume in 1 second; CI: confidence interval; MMRM: mixed model with repeated measurements; MD: mean difference; MV: mean value; N: number of evaluated patients; RCT: Randomised Controlled Study; SD: standard deviation; VAS: visual analogue scale.

Study VX08-770-103: Ivacaftor + BSC vs placebo + BSC

Endpoint category Endpoint	Ivacaftor + BSC		Placebo + BSC		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Side effects					
AE (additionally shown)	20	20 (100.0)	18	17 (94.4)	–
SAE[a]	not usable[b]				
Discontinuation because of AE	20	0 (0)	18	1 (5.6)	0.30 [0.01; 6.97]; 0.353[c, d]
Rash (PT, AE)	no data available	no data available	no data available	no data available	no data available
Dizziness (PT, AE)	no data available	no data available	no data available	no data available	no data available

a: When the AEs were assessed, events of the underlying disease, including pulmonary exacerbation events, were also assessed via the PT "cystic fibrosis of the lung"; see section 2.7.4.3.2. of dossier evaluation A19-65 of the IQWiG
b: Data are not usable, because there is no information on the type of events contained in the data for the relevant sub-population. In the total population, a relevant proportion of patients with events of the PT "cystic fibrosis of the lungs" as well as events that can be both side effects and symptomatology of the disease is included.
c: RR and CI Calculation of the IQWiG. p value calculation of the IQWiG, unconditional exact test (CSZ method)
d: Calculation of the IQWiG with continuity correction

BSC: best supportive care; CF: cystic fibrosis; CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of patients with at least one dose of the study medication, considered as treated, not randomised; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No differences relevant for the benefit assessment.
Morbidity	↑	Advantage in BMI z-score as well as advantages taking into consideration the results in patients aged 12 years and older
Health-related quality of life	↑	Advantages taking into consideration the results in patients aged 12 years and older
Side effects	↔	No differences relevant for the benefit assessment. Data on SAE are not usable.
Explanations: ↑, ↓: statistically significant and relevant positive or negative effect with high or unclear risk of bias ↑↑, ↓↓: statistically significant and relevant positive or negative effect with low risk of bias ↔: no relevant difference ∅: no data available n.a.: not assessable		

b) Patients aged 12 years and older with cystic fibrosis with a G551D mutation in the *CFTR* gene

Study VX08-770-102: Ivacaftor + BSC vs placebo + BSC

Endpoint category Endpoint	Ivacaftor + BSC		Placebo + BSC		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Mortality					
No deaths occurred					

Endpoint category Endpoint	Ivacaftor + BSC		Placebo + BSC		Group difference
	N	Number of events n_E (n_E/patient years)[a]	N	Number of events n_E (n_E/patient years)[a]	Rate ratio [95% CI]; p value
Morbidity					
Pulmonary exacerbations	83	47 (0.63[b])	78	99 (1.48[b])	0.43 [0.27; 0.68]; < 0.001[c]
Hospitalisations because of pulmonary exacerbations	83	21 (0.28[b])	78	31 (0.46[b])	0.64 [0.32; 1.26]; 0.195[c]

a: Event rate (n_E/patient years) is calculated by dividing the total number of events by the total number of years (sum of time in the study of all patients included in the analysis)
b: Calculation of the IQWiG
c: Negative binomial model
BSC: best supportive care; CI: confidence interval; n: number of patients with (at least 1) event; N: number of patients with at least one dose of the study medication; n_E: number of events; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event.

Study VX08-770-102: Ivacaftor + BSC vs placebo + BSC

Endpoint category Endpoint	Ivacaftor + BSC			Placebo + BSC			Group difference
	N[a]	Values at start of study MV (SD)	Change at the end of study[b] MV (SD)	N[a]	Values at start of study MV (SD)	Change at the end of study[b] MV (SD)	MD [95% CI]; p value[c]
Morbidity							
FEV_1[i]							
FEV_1 (absolute change) %[d]	83	63.46 (16.14)	9.42 (8.31)	78	63.67 (16.83)	−1.24 (7.70)	10.50 [8.50; 12.50]; < 0.001
FEV_1 (relative change) %[d]	83	63.46 (16.14)	15.42 (14.35)	78	63.67 (16.83)	−1.77 (12.88)	17.01 [13.84; 21.19]; < 0.001
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[d]							
CFQ-R, domains on symptomatology[d]							
Respiratory system[j]	80	70.21 (16.40)	6.39 (16.81)	71	68.97 (19.17)	−3.93 (14.21)	8.60 [5.32; 11.87]; < 0.001 Hedges' g: 0.84 [0.50; 1.17]
Gastrointestinal symptoms[j]	80	85.15 (12.98)	0.60 (14.10)	70	85.81 (18.38)	−1.79 (14.25)	0.48 [−2.29; 3.25]; 0.732
Weight problems[k]	76	78.95 (30.72)	8.33 (25.48)	64	78.79 (31.84)	−4.02 (30.00)	5.28 [−0.08; 10.63]; 0.053
Health status							
EQ5D-VAS[d]	76	77.70 (15.07)	3.06 (16.09)	65	78.83 (13.95)	−0.78 (10.34)	3.96 [−0.23; 8.14]; 0.064[f]
BMI[l] ([kg/m²] absolute change)	83	21.74 (3.65)	1.00 (1.60)	78	21.88 (3.49)	−0.05 (1.02)	0.93 [0.48; 1.38] < 0.001[g]
BMI[l] (age dependent z-score, absolute change)	24[h]	−0.47 (0.92)	0.33 (0.57)	23[h]	−0.56 (0.78)	−0.11 (0.46)	0.33 [0.002; 0.65]; 0.049[g]
Sweat chloride concentration (additionally shown) [m]							
Absolute change at Week 48[mmol/l]	78[n]	100.35 (10.00)	−49.75 (17.34)	74[n]	100.13 (10.63)	1.30 (9.02)	−50.93 [−55.55; −46.32]; < 0.001

Study VX08-770-102: Ivacaftor + BSC vs placebo + BSC

Endpoint category Endpoint	Ivacaftor + BSC			Placebo + BSC			Group difference
	N[a]	Values at start of study MV (SD)	Change at the end of study[b] MV (SD)	N[a]	Values at start of study MV (SD)	Change at the end of study[b] MV (SD)	MD [95% CI]; p value[c]
Health-related quality of life							
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[d]							
CFQ-R, domains on health-related quality of life							
Physical well-being[j]	80	76.10 (24.13)	5.96 (15.42)	70	80.61 (22.14)	−4.63 (17.22)	4.44 [1.33; 7.55] 0.006 Hedges' g: 0.42 [0.10; 0.75]
Effect modification by Feature FEV_1 % of the standardised normal value at the start of study							
< 70%	47	70.26 (24.42)	4.76 (14.78)	39	73.02 (24.79)	−5.15 (16.98)	8.35 [3.95; 12.75] < 0.001 Hedges'g 0.75 [0.31; 1.19]
≥ 70%	33	84.43 (21.43)	7.94 (16.50)	31	90.09 (13.51)	−3.96 (17.83)	−2.07 [−5.46; 1.32] 0.227
Emotional state[j]	80	86.02 (13.95)	1.59 (12.56)	70	83.95 (15.86)	−1.40 (11.08)	2.12 [−0.38; 4.63]; 0.096
Vitality[k]	76	64.25 (16.26)	2.08 (17.73)	64	65.53 (18.88)	−3.88 (15.71)	5.45 [1.97; 8.94]; 0.002 Hedges' g: 0.50 [0.17; 0.84]
Effect modification by Feature FEV_1 % of the standardised normal value at the start of study							
< 70%	46	64.31 (16.17)	−0.74 (19.20)	36	63.28 (19.19)	−6.31 (15.32)	9.06 [3.92; 14.19] < 0.001 Hedges'g 0.77 [0.31; 1.22]
≥ 70%	30	64.17 (16.69)	6.79 (14.06)	28	68.39 (18.42)	−0.66 (15.94)	0.85 [−3.60; 5.30] 0.702
Social limitations[j]	80	72.11 (16.43)	4.79 (13.69)	70	72.47 (17.96)	−1.50 (12.14)	4.25 [1.52; 6.98]; 0.003 Hedges' g: 0.48 [0.16; 0.81]
Role function[k]	76	86.30 (13.52)	1.38 (14.93)	64	85.99 (15.76)	−3.45 (17.31)	−0.58 [−3.10; 1.94]; 0.651
Body image[j]	80	80.98 (20.17)	3.00 (14.51)	70	80.88 (21.03)	−2.51 (17.23)	2.70 [−0.38; 5.77]; 0.086
Eating disorders[j]	80	91.81 (14.11)	3.45 (15.15)	70	91.98 (15.62)	−2.33 (15.21)	3.34 [1.23; 5.44]; 0.002 Hedges' g: 0.50 [0.17; 0.83]
Burden of therapy[j]	80	64.46 (19.73)	6.15 (17.06)	70	65.76 (17.67)	−0.72 (14.05)	3.31 [0.12; 6.50]; 0.042 Hedges' g: 0.32 [−0.01; 0.64]

Study VX08-770-102: Ivacaftor + BSC vs placebo + BSC

Endpoint category Endpoint	Ivacaftor + BSC			Placebo + BSC			Group difference
	N[a]	Values at start of study MV (SD)	Change at the end of study[b] MV (SD)	N[a]	Values at start of study MV (SD)	Change at the end of study[b] MV (SD)	MD [95% CI]; p value[c]
Health-related quality of life							
Cystic Fibrosis Questionnaire-Revised (CFQ-R)[d]							
Subjective perception of health[k]	76	72.09 (18.91)	5.40 (18.36)	64	72.07 (18.93)	−5.74 (16.15)	7.57 [4.41; 10.73]; < 0.001 Hedges' g: 0.75 [0.41; 1.10]

a: Number of patients considered in MMRM to calculate the effect estimate; the values at the start of study may be based on more patients and the values at the end of study on fewer patients.
b: Refers to the change from the start of study at the last time of measurement
c: MMRM; effect represents the difference between the treatment groups in the changes averaged over the course of the study between the respective measurement time and the start of study. Model: dependent variable absolute change (or relative change for "FEV_1, relative change") from baseline; time of study and treatment as fixed effects; adjusted for continuous baseline values age, FEV_1 (as % of standardised normal value), and – for CFQ-R domains – CFQ-R domain score.
d: For FEV_1 as % of the standardised normal value; higher values mean a better function, health-related quality of life or symptomatology; a positive group difference corresponds to an advantage for ivacaftor.
e: According to the study report, all but one patient on the placebo arm were included in the evaluation of the total population (over the entire study period). The statement of the pharmaceutical company regarding the evaluation of the sub-population – i.e. that 4 of 18 patients are missing in the placebo arm – is therefore implausible. An N of 17 is assumed.
f: MMRM; effect represents the difference between the treatment groups of the changes from the start of study at week 48. Model: dependent variable: absolute change from baseline; treatment×time of study, time of study, and treatment as fixed effects; adjusted for continuous baseline values of age (for FEV_1, only in Study VX08-770-102), EQ-5D VAS score, and FEV_1 (as % of standardised normal value). Further adjustment according to continuous baseline values: At BMI (z-score) according to BMI (z-score).
g: Linear mixed mode; effect represents the difference between the treatment groups of the changes from the start of study at week 48. Model: dependent variable absolute change from baseline; treatment as fixed effect, treatment×time of study, time of study, treatment and intercept as random effects; adjusted for baseline values of age group and FEV_1 category (as % of standardised normal value).
h: Based on participants at the age of ≤ 20 years N = 24 (ivacaftor + BSC) vs N = 23 (placebo + BSC)
i: Primary endpoint of the Study VX08-770-102
j: Children 12 to 13 years and adolescents or adults, pooled
k: Only for adolescents or adults; not intended for children [12 to 13 years].
l: Absolute change
m: Data from the dossier of the pharmaceutical company.
n: Values at the start of study. The values at the end of study can be based on fewer patients.

BMI: Body Mass Index; BSC: best supportive care; BMI: Body Mass Index; CFQ-R: Cystic Fibrosis Questionnaire-Revised; EQ-5D: European Quality of Life Questionnaire 5 Dimensions; FEV_1: forced expiratory volume in 1 second; CI: confidence interval; MMRM: mixed model with repeated measurements; MD: mean difference; MV: mean value; N: number of evaluated patients; RCT: Randomised Controlled Study; SD: standard deviation; VAS: visual analogue scale.

Study VX08-770-102: Ivacaftor + BSC vs placebo + BSC

Endpoint category Endpoint	Ivacaftor + BSC		Placebo + BSC		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Side effects					
AE (additionally shown)	83	82 (98.8)	78	78 (100.0)	–
SAE[a]	not usable[b]				
Discontinuation because of AE	83	1 (1.2)	78	4 (5.1)	0.23 [0.03; 2.06]; 0.153[c]
Rash (PT, AE)	83	12 (14.5)	78	4 (5.1)	2.82 [0.95; 8.37]; 0.049[d, e]
Dizziness (PT, AE)	83	10 (12.0)	78	1 (1.3)	9.40 [1.23; 71.72]; 0.007[d]

a: When the AEs were assessed, events of the underlying disease, including pulmonary exacerbation events, were also assessed via the PT “cystic fibrosis of the lung”; see section 2.7.4.3.2. of dossier evaluation A19-65 of the IQWiG
b: Data are not usable because a large proportion of patients with events of the PT “cystic fibrosis of the lungs” as well as events that can be both side effects and symptomatology of the disease is included.
c: Mantel and Haenszel, unstratified
d: RR and CI Calculation of the IQWiG. p value calculation of the IQWiG, unconditional exact test (CSZ method)
f: Calculation of the IQWiG with continuity correction
e: Discrepancy between p value (exact) and CI (asymptotic) because of different calculation methods.
BSC: best supportive care; CF: cystic fibrosis; CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of patients with at least one dose of the study medication, considered as treated, not randomised; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No differences relevant for the benefit assessment.
Morbidity	↑	Advantage in respiratory system symptomatology
Health-related quality of life	↑	Advantages in physical well-being as well as vitality and subjective perception of health in patients with FEV_1 < 70% at the start of study
Side effects	↔	No differences relevant for the benefit assessment. Data on SAE are not usable.

Explanations:
↑, ↓: statistically significant and relevant positive or negative effect with high or unclear risk of bias
↑↑, ↓↓: statistically significant and relevant positive or negative effect with low risk of bias
↔: no relevant difference
∅: no data available
n.a.: not assessable

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

a) Patients aged 6 to 11 years with cystic fibrosis with a G551D mutation in the *CFTR* gene

30 patients

b) Patients aged 12 years and older with cystic fibrosis with a G551D mutation in the *CFTR* gene

180 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Kalydeco® (active ingredient: ivacaftor) at the following publicly accessible link (last access: 5 February 2020):
https://www.ema.europa.eu/documents/product-information/kalydeco-epar-product-information_de.pdf

Treatment with ivacaftor should only be initiated and monitored by specialists who are experienced in the treatment of patients with cystic fibrosis.

4. Treatment costs

Annual treatment costs:

a) Patients aged 6 to 11 years with cystic fibrosis with a G551D mutation in the *CFTR* gene

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ivacaftor	€ 201,955.67
Best supportive care	different for each individual patient
Appropriate comparator therapy:	
Best supportive care	different for each individual patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2020

b) Patients aged 12 years and older with cystic fibrosis with a G551D mutation in the *CFTR* gene

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ivacaftor	€ 201,955.67
Best supportive care	different for each individual patient
Appropriate comparator therapy:	
Best supportive care	different for each individual patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2020

Costs for additionally required SHI services: not applicable