IQWiG Reports – Commission No. A20-05

Ivacaftor (combination with tezacaftor/ivacaftor; cystic fibrosis, 12 years and older, with F508del mutation, homozygous) –

Addendum to Commission A19-70[1]

Addendum

Commission: A20-05
Version: 1.0
Status: 30 January 2020

[1] Translation of addendum A20-05 *Ivacaftor (Kombination mit Tezacaftor/Ivacaftor; zystische Fibrose, ab 12 Jahre, F508del-Mutation, homozygot) – Addendum zum Auftrag A19-70* (Version 1.0; Status: 30 January 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Ivacaftor (combination with tezacaftor/ivacaftor; cystic fibrosis, 12 years and older, with F508del mutation, homozygous) – Addendum to Commission A19-70

Commissioning agency

Federal Joint Committee

Commission awarded on

7 January 2020

Internal Commission No.

A20-05

Address of publisher

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Keywords: Ivacaftor, Tezacaftor, Cystic Fibrosis, Child, Adolescent, Adult, Benefit Assessment, NCT01807923, NCT01807949, NCT02347657

Table of contents

Page

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
AE	adverse event
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SOC	System Organ Class

1 Background

On 7 January 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-70 (Ivacaftor – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier, the pharmaceutical company (hereinafter referred to as "the company") presented results of an adjusted indirect comparison on the basis of the randomized controlled trials (RCTs) VX14-661-106 (study with ivacaftor + tezacaftor/ivacaftor), VX12-809-103 and VX12-809-104 (studies with lumacaftor/ivacaftor) for the assessment of the added benefit of ivacaftor in combination with tezacaftor/ivacaftor in patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This adjusted indirect comparison (see Figure 1) was used for the benefit assessment.

In its dossier [2], the company had presented analyses for the outcomes "serious adverse events (SAEs)" and "discontinuation due to adverse events (AEs)". The results of these outcomes contained events that can be both symptoms of the underlying disease (particularly pulmonary exacerbation events) and side effects. As a result, the data for the outcome "SAEs" were not usable in dossier assessment A19-70. Regarding the outcome "discontinuation due to AEs", there was a high risk of bias, as shifting of the effect estimation caused by the recording of the underlying disease could not be excluded due to the overall low number of events leading to discontinuation of the study medication.

The G-BA commissioned IQWiG to present and assess the analyses on the outcomes "SAEs" and "discontinuation due to AEs" without pulmonary exacerbations presented by the company in the comments, under consideration of the information provided in the dossier.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The company had presented analyses on the basis of an indirect comparison (see Figure 1) in its dossier for the assessment of ivacaftor in combination with tezacaftor/ivacaftor in patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. For the outcomes "SAEs" and "discontinuation due to AEs", the company had shown analyses that contained events that form part of the symptoms of the underlying disease or that can be both side effects and symptoms of the underlying disease.

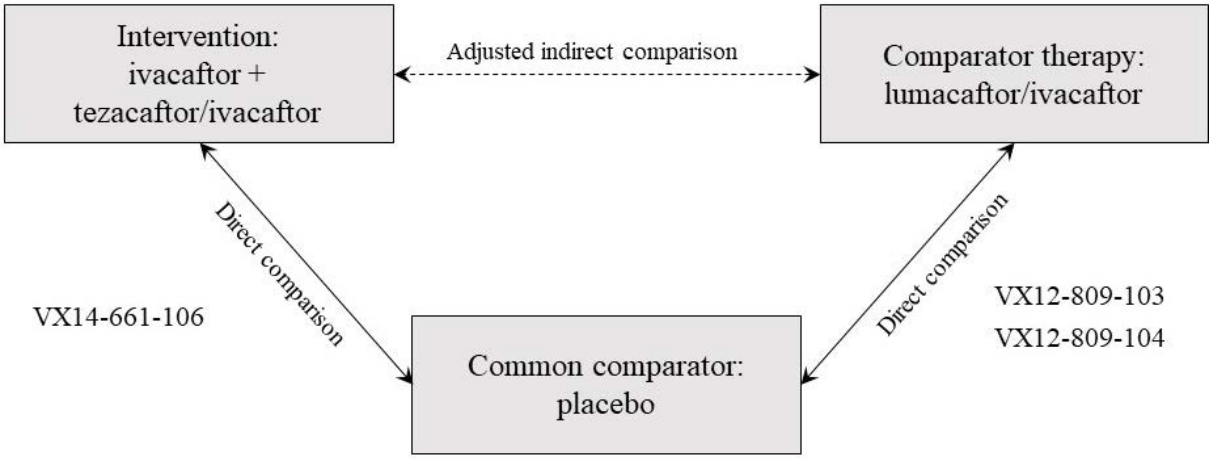

Figure 1: Study pool for the indirect comparison between ivacaftor + tezacaftor/ivacaftor and the ACT lumacaftor/ivacaftor

As already described in dossier assessment A19-70, an adequate operationalization of the outcomes "SAEs" and "discontinuation due to AEs" is an analysis without events of the underlying disease. This applies to events that form part of the symptoms of the underlying disease or that can be both side effects or symptoms of the underlying disease. The Preferred Term (PT) "infective pulmonary exacerbation of cystic fibrosis" was mentioned as an example in dossier assessment A19-70 [1] because here the allocation to the underlying disease is clear and this PT was rated to a relevant extent as SAE or discontinuation due to AEs in the studies.

With its comments [3,4], the company presented additional analyses on SAEs and discontinuation due to AEs without the PT "infective pulmonary exacerbation of cystic fibrosis".

2.1 Risk of bias

The risk of bias for the outcome "SAEs" was rated as high for the results from the studies included in the adjusted indirect comparison. The analyses on SAEs subsequently submitted by the company did not contain the PT "infective pulmonary exacerbation of cystic fibrosis", and therefore a large proportion of events that can be allocated to the underlying disease were not included in the analysis. However, further events occurred that could potentially be allocated to the underlying disease, such as the PTs "haemoptysis", "pneumonia" or "distal intestinal obstruction syndrome/ileus", for example. Neither in Module 4 of its dossier nor in its

comments did the company address the influence possible further events that can be allocated to symptoms of the underlying disease might have on the effect estimations. For the present assessment, all System Organ Classes (SOCs) and PTs can be found in Appendix B for all 3 studies of the indirect comparison, without threshold values for a minimum frequency.

The risk of bias for the outcome “discontinuation due to AEs” was not assessed because the data presented by the company were not usable (see Section 2.2 for more information).

2.2 Results

The following Table 1 shows the results from the studies for the adjusted indirect comparison in patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene for the outcomes “SAEs” and “discontinuation due to AEs” without consideration of the PT “infective pulmonary exacerbation of cystic fibrosis” in the analysis.

Table 1: Results (side effects, dichotomous) – RCT, indirect comparison using common comparators: ivacaftor + tezacaftor/ivacaftor vs. lumacaftor/ivacaftor:

Outcome category **Outcome** **Comparison** **Study**	**Ivacaftor + tezacaftor/ivacaftor[a] or lumacaftor/ivacaftor[a]**		**Placebo[a]**		**Group difference**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
Side effects					
SAEs[b]					
Ivacaftor + tezacaftor/ivacaftor vs. placebo					
VX14-661-106	251	14 (5.6)	258	26 (10.1)	0.55 [0.30; 1.04]; 0.064
Lumacaftor/ivacaftor vs. placebo					
VX12-809-103	182	19 (10.4)	184	15 (8.2)	1.28 [0.67; 2.44]; 0.453
VX12-809-104	187	10 (5.3)	186	17 (9.1)	0.59 [0.28; 1.24]; 0.164
Total[c]					0.92 [0.56; 1.50]; 0.738
Indirect comparison using common comparators[d]:					-[e]
Discontinuation due to AEs[b]					
Ivacaftor + tezacaftor/ivacaftor vs. placebo					
VX14-661-106[f]	251	ND	258	8 (3.1)	0.77 [0.27; 2.19]; 0.625
Lumacaftor/ivacaftor vs. placebo					
VX12-809-103[f]	182	6 (3.3)	184	4 (2.2)	1.52 [0.44; 5.28]; 0.513
VX12-809-104[f]	187	ND	186	2 (1.1)	ND
Total[c]					2.38 [0.84; 6.78]; 0.083
Indirect comparison using common comparators[d]:					-[g]

a. Treatment was against the background of concomitant symptomatic treatment.
b. Without recording of the PT "infective pulmonary exacerbation of cystic fibrosis".
c. Model with fixed effect.
d. Indirect comparison according to Bucher [5].
e. No presentation of the effect estimate, as there is only one study, which has an outcome-specific high risk of bias, on the intervention side of the indirect comparison, which results in an insufficient certainty of results of the effect estimation for this outcome. No hint of greater or lesser harm is derived.
f. The company did not process the number of patients with discontinuation due to AEs without discontinuation due to pulmonary exacerbations (PT). The table presents the numbers of patients with discontinuation due to AEs if it can be inferred from the available documents that no patient was documented with the PT "infective pulmonary exacerbation of cystic fibrosis".
g. No usable data. There is no information on patients with discontinuation due to AEs without consideration of the PT "infective pulmonary exacerbation of cystic fibrosis" in 2 studies, no information of the effect estimate for one of the studies on the comparator intervention and no information on the check of homogeneity of the studies on the comparator intervention.

CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Serious adverse events

All 3 studies of the indirect comparison have a high risk of bias for the outcome "SAEs" (see Section 2.1). Since there is therefore only one study, which additionally has an outcome-specific high risk of bias, on the intervention side of the indirect comparison, there is an insufficient certainty of results of the effect estimation for this outcome. Hence, there is no hint of greater or lesser harm of ivacaftor + tezacaftor/ivacaftor versus lumacaftor/ivacaftor for the outcome "SAEs" (without consideration of the PT "infective pulmonary exacerbation of cystic fibrosis"); an added benefit is therefore not proven.

As supplementary information for the outcome "SAEs", the effect estimate from the adjusted indirect comparison of ivacaftor + tezacaftor/ivacaftor with lumacaftor/ivacaftor provided by the company is presented in Appendix A.

Discontinuation due to adverse events

The analyses on the outcome "discontinuation due to AEs" without consideration of the PT "infective pulmonary exacerbation of cystic fibrosis" subsequently submitted by the company were not usable. The company submitted incomplete data. There was no information on the number of patients with discontinuation due to AEs (without consideration of the PT "infective pulmonary exacerbation of cystic fibrosis"). Besides, the effect estimate at study level was missing for the VX12-809-104 study (lumacaftor/ivacaftor versus placebo) as well as information on heterogeneity for the pooled effect estimate from both studies on lumacaftor/ivacaftor versus placebo. Since this information was lacking, the check of homogeneity, a prerequisite for conducting the adjusted indirect comparison, cannot be verified. Hence, there is no hint of greater or lesser harm of ivacaftor + tezacaftor/ivacaftor versus lumacaftor/ivacaftor for the outcome "discontinuation due to AEs" (without consideration of the PT "infective pulmonary exacerbation of cystic fibrosis"); an added benefit is therefore not proven.

As supplementary information for the outcome "discontinuation due to AEs", the effect estimate from the adjusted indirect comparison of ivacaftor + tezacaftor/ivacaftor with lumacaftor/ivacaftor presented by the company is presented in Appendix A.

2.3 Summary

The data on the outcomes "SAEs" and "discontinuation due to AEs" subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of ivacaftor in combination with tezacaftor/ivacaftor from dossier assessment A19-70.

The following Table 2 shows the result of the benefit assessment of ivacaftor + tezacaftor/ivacaftor under consideration of dossier assessment A19-70 and the present addendum.

Table 2: Ivacaftor + tezacaftor/ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[b]**
CF patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor	Hint of lesser benefit
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

3 References

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Appendix A – Results on SAEs and discontinuation due to AEs from the indirect comparison

Table 3: Results (side effects, dichotomous) – RCT, indirect comparison using common comparators: ivacaftor + tezacaftor/ivacaftor vs. lumacaftor/ivacaftor

Outcome category **Outcome** **Comparison** **Study**	**Ivacaftor + tezacaftor/ivacaftor[a] or lumacaftor/ivacaftor[a]**		**Placebo[a]**		**Group difference**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
Side effects					
SAEs[b]					
Ivacaftor + tezacaftor/ivacaftor vs. placebo					
VX14-661-106	251	14 (5.6)	258	26 (10.1)	0.55 [0.30; 1.04]; 0.064
Lumacaftor/ivacaftor vs. placebo					
VX12-809-103	182	19 (10.4)	184	15 (8.2)	1.28 [0.67; 2.44]; 0.453
VX12-809-104	187	10 (5.3)	186	17 (9.1)	0.59 [0.28; 1.24]; 0.164
Total[c]					0.92 [0.56; 1.50]; 0.738
Indirect comparison using common comparators (supplementary presentation, not interpretable)[d]:					0.60 [0.27; 1.33]; ND
Discontinuation due to AEs[b]					
Ivacaftor + tezacaftor/ivacaftor vs. placebo					
VX14-661-106[e]	251	ND	258	8 (3.1)	0.77 [0.27; 2.19]; 0.625
Lumacaftor/ivacaftor vs. placebo					
VX12-809-103[e]	182	6 (3.3)	184	4 (2.2)	1.52 [0.44; 5.28]; 0.513
VX12-809-104[e]	187	ND	186	2 (1.1)	ND
Total[c]					2.38 [0.84; 6.78]; 0.083
Indirect comparison using common comparators (supplementary presentation, not interpretable)[d]:					0.33 [0.08; 1.36]; ND

a. Treatment was against the background of concomitant symptomatic treatment.
b. Without recording of the PT "infective pulmonary exacerbation of cystic fibrosis".
c. Model with fixed effect.
d. Indirect comparison according to Bucher [5].
e. The company did not process the number of patients with discontinuation due to AEs without discontinuation due to pulmonary exacerbations (PT). The table presents the numbers of patients with discontinuation due to AEs if it can be inferred from the available documents that no patient was documented with the PT "infective pulmonary exacerbation of cystic fibrosis".

CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Appendix B – SAEs of the studies VX12-809-103, VX12-809-104 and VX14-661-106

Table 4: SAEs – RCT, indirect comparison: lumacaftor/ivacaftor vs. placebo (study VX12-809-103) (multipage table)

SOC[a] PT[a]	Patients with event n (%)	
	Lumacaftor/ ivacaftor[b] N = 182	Placebo N = 184[b]
Overall rate of SAEs	33 (18.1)	49 (26.6)
Infections and infestations	19 (10.4)	44 (23.9)
Infective pulmonary exacerbation of cystic fibrosis	17 (9.3)	41 (22.3)
Influenza	0 (0)	1 (0.5)
Tracheobronchitis	1 (0.5)	1 (0.5)
Kidney infection	1 (0.5)	0 (0)
Urinary tract infection	1 (0.5)	0 (0)
Appendicitis	0 (0)	1 (0.5)
Bronchopneumonia	0 (0)	1 (0.5)
Infective exacerbation of bronchiectasis	0 (0)	1 (0.5)
Lung infection	0 (0)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	8 (4.4)	2 (1.1)
Haemoptysis	5 (2.7)	2 (1.1)
Cough	1 (0.5)	0 (0)
Lung disorder	1 (0.5)	0 (0)
Pneumomediastinum	1 (0.5)	0 (0)
Pneumothorax	1 (0.5)	0 (0)
Gastrointestinal disorders	4 (2.2)	3 (1.6)
Distal intestinal obstruction syndrome	2 (1.1)	2 (1.1)
Constipation	1 (0.5)	1 (0.5)
Lower gastrointestinal haemorrhage	1 (0.5)	0 (0)
Investigations	2 (1.1)	1 (0.5)
Forced expiratory volume decreased	1 (0.5)	0 (0)
Alanine aminotransferase increased	1 (0.5)	0 (0)
Aspartate aminotransferase increased	1 (0.5)	0 (0)
Gamma-glutamyltransferase increased	1 (0.5)	0 (0)
Blood alkaline phosphatase increased	0 (0)	1 (0.5)
Immune system disorders	1 (0.5)	0 (0)
Drug hypersensitivity	1 (0.5)	0 (0)
Injury, poisoning and procedural complications	1 (0.5)	0 (0)
Post procedural haematoma	1 (0.5)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	2 (1.1)
Seminoma	1 (0.5)	0 (0)
Colon cancer metastatic	0 (0)	1 (0.5)
Renal cancer	0 (0)	1 (0.5)

Table 4: SAEs – RCT, indirect comparison: lumacaftor/ivacaftor vs. placebo (study VX12-809-103) (multipage table)

SOC[a] **PT[a]**	**Patients with event n (%)**	
	Lumacaftor/ ivacaftor[b] N = 182	**Placebo N = 184[b]**
Nervous system disorders	1 (0.5)	0 (0)
Epilepsy	1 (0.5)	0 (0)
Renal and urinary disorders	1 (0.5)	0 (0)
Nephrolithiasis	1 (0.5)	0 (0)
Skin and subcutaneous tissue disorders	1 (0.5)	0 (0)
Rash	1 (0.5)	0 (0)
Metabolism and nutrition disorders	0 (0)	1 (0.5)
Diabetes mellitus inadequate control	0 (0)	1 (0.5)
Vascular disorders	0 (0)	1 (0.5)
Deep vein thrombosis	0 (0)	1 (0.5)

a. MedDRA version 17.0.
b. Treatment was against the background of concomitant symptomatic treatment.

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

Table 5: SAEs – RCT, direct comparison: lumacaftor/ivacaftor vs. placebo (study VX12-809-104) (multipage table)

SOC[a] **PT[a]**	**Patients with event n (%)**	
	Lumacaftor/ ivacaftor[b] N = 187	**Placebo N = 186[b]**
Overall rate of SAEs	31 (16.6)	57 (30.6)
Infections and infestations	26 (13.9)	50 (26.9)
Infective pulmonary exacerbation of cystic fibrosis	24 (12.8)	48 (25.8)
Bronchopneumonia	1 (0.5)	0 (0)
Bronchitis	0 (0)	2 (1.1)
Gastroenteritis viral	1 (0.5)	0 (0)
Pneumonia	1 (0.5)	0 (0)
Influenza	0 (0)	1 (0.5)
Viraemia	0 (0)	1 (0.5)
Viral infection	0 (0)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	0 (0)	1 (0.5)
Haemoptysis	0 (0)	1 (0.5)

Table 5: SAEs – RCT, direct comparison: lumacaftor/ivacaftor vs. placebo (study VX12-809-104) (multipage table)

SOC[a] **PT[a]**	**Patients with event n (%)**	
	Lumacaftor/ ivacaftor[b] **N = 187**	**Placebo** **N = 186[b]**
Investigations	4 (2.1)	0 (0)
Blood creatine phosphokinase increased	2 (1.1)	0 (0)
Liver function test abnormal	1 (0.5)	0 (0)
Bacterial test positive	1 (0.5)	0 (0)
Electrocardiogram T wave inversion	1 (0.5)	0 (0)
Gastrointestinal disorders	1 (0.5)	5 (2.7)
Constipation	0 (0)	1 (0.5)
Ileus	1 (0.5)	0 (0)
Abdominal pain	0 (0)	1 (0.5)
Distal intestinal obstruction syndrome	0 (0)	3 (1.6)
Nervous system disorders	2 (1.1)	0 (0)
Convulsion	1 (0.5)	0 (0)
Hepatic encephalopathy	1 (0.5)	0 (0)
Renal and urinary disorders	0 (0)	3 (1.6)
Nephrolithiasis	0 (0)	2 (1.1)
Proteinuria	0 (0)	1 (0.5)
Renal failure acute	0 (0)	1 (0.5)
Vascular disorders	0 (0)	2 (1.1)
Axillary vein thrombosis	0 (0)	1 (0.5)
Deep vein thrombosis	0 (0)	1 (0.5)
Musculoskeletal and connective tissue disorders	0 (0)	1 (0.5)
Arthralgia	0 (0)	1 (0.5)
Psychiatric disorders	0 (0)	2 (1.1)
Suicidal ideation	0 (0)	1 (0.5)
Suicide attempt	0 (0)	1 (0.5)

a. MedDRA version 17.0.
b. Treatment was against the background of concomitant symptomatic treatment.

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

Table 6: SAEs – RCT, direct comparison: ivacaftor + tezacaftor/ivacaftor vs. placebo (study VX14-661-106) (multipage table)

SOC[a] **PT[a]**	**Patients with event n (%)**	
	Ivacaftor + tezacaftor/ivacaftor[b] **N = 251**	**Placebo[b]** **N = 258**
Overall rate of SAEs		
Infections and infestations	25 (10)	36 (14.0)
Infective pulmonary exacerbation of cystic fibrosis	23 (9.2)	32 (12.4)
Pneumonia	2 (0.8)	1 (0.4)
Clostridium difficile colitis	1 (0.4)	0 (0)
Lung abscess	1 (0.4)	0 (0)
Virus infection of the respiratory tract	1 (0.4)	0 (0)
Acarodermatitis	0 (0)	1 (0.4)
Bronchitis	0 (0)	1 (0.4)
Bronchopulmonary aspergillosis allergic	0 (0)	1 (0.4)
Gastroenteritis viral	0 (0)	1 (0.4)
Influenza	0 (0)	1 (0.4)
Nervous system disorders	3 (1.2)	1 (0.4)
Benign intracranial hypertension	1 (0.4)	0 (0)
Generalized tonic-clonic seizure	1 (0.4)	0 (0)
Migraine	1 (0.4)	0 (0)
Headache	0 (0)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	3 (1.2)	5 (1.9)
Haemoptysis	3 (1.2)	3 (1.2)
Cough	0 (0)	1 (0.4)
Paranasal cyst	0 (0)	1 (0.4)
Gastrointestinal disorders	1 (0.4)	6 (2.3)
Inguinal hernia	1 (0.4)	0 (0)
Coeliac disease	0 (0)	1 (0.4)
Constipation	0 (0)	2 (0.8)
Faecaloma	0 (0)	1 (0.4)
Gastric ulcer	0 (0)	1 (0.4)
Gastritis	0 (0)	1 (0.4)
Pancreatitis acute	0 (0)	1 (0.4)
Investigations	1 (0.4)	4 (1.6)
Blood creatine phosphokinase increased	1 (0.4)	1 (0.4)
Blood glucose abnormal	0 (0)	1 (0.4)
Electrocardiogram ST segment elevation	0 (0)	1 (0.4)
Pulmonary function test decreased	0 (0)	1 (0.4)
Musculoskeletal and connective tissue disorders	1 (0.4)	0 (0)
Musculoskeletal chest pain	1 (0.4)	0 (0)

Table 6: SAEs – RCT, direct comparison: ivacaftor + tezacaftor/ivacaftor vs. placebo (study VX14-661-106) (multipage table)

SOC[a] **PT[a]**	**Patients with event n (%)**	
	Ivacaftor + tezacaftor/ivacaftor[b] **N = 251**	**Placebo[b]** **N = 258**
Blood and lymphatic system disorders	0 (0)	1 (0.4)
Haemolytic anaemia	0 (0)	1 (0.4)
General disorders and administration site conditions	0 (0)	2 (0.8)
Chest discomfort	0 (0)	1 (0.4)
Fatigue	0 (0)	1 (0.4)
Injury, poisoning and procedural complications	0 (0)	2 (0.8)
Alcohol poisoning	0 (0)	1 (0.4)
Toxicity to various agents	0 (0)	1 (0.4)
Wrist fracture	0 (0)	1 (0.4)
Renal and urinary disorders	0 (0)	2 (0.8)
Acute kidney injury	0 (0)	2 (0.8)

a. MedDRA version 17.0.
b. Treatment was against the background of concomitant symptomatic treatment.

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