

SUPPLEMENTAL MATERIALS. Effect of Elexacaftor/Tezacaftor/Ivacaftor Treatment on Extrapulmonary Complications of Cystic Fibrosis

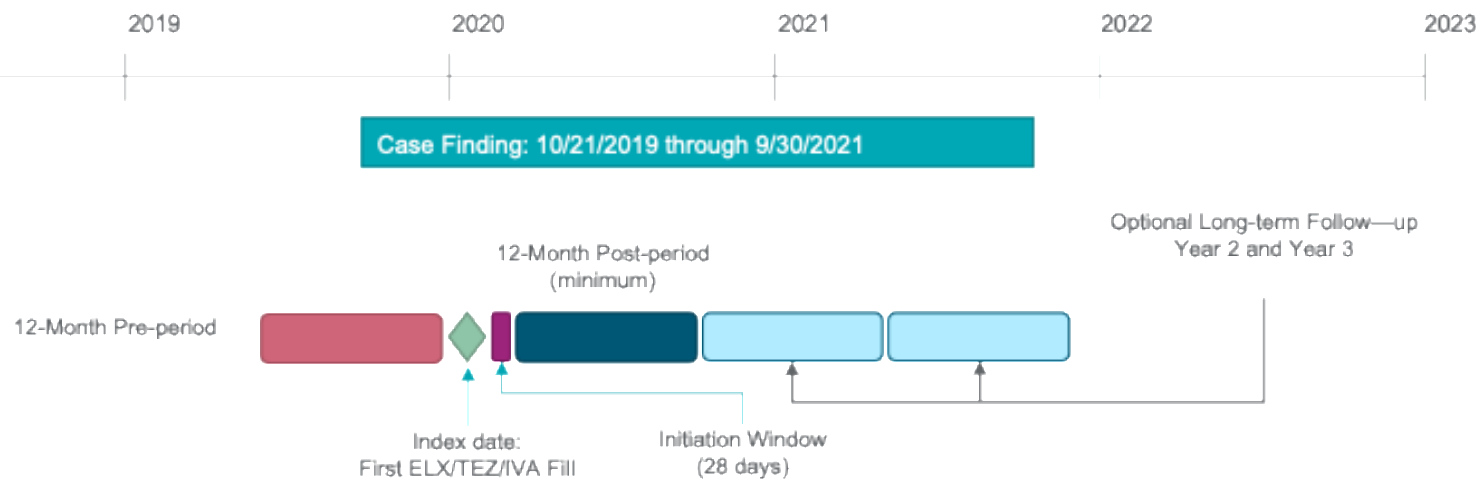
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10 **Figure E1. Study Diagram**



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13 The 28-day initiation window + the follow-up period = 392 days for the 1-year follow-up period, and 1,122 days for the 3-year follow-up period.

14 ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor.

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23 **Table E1.** Extrapulmonary Complication Definitions and Associated Codes

Extrapulmonary Complications				
Complication system	Diagnoses	ICD-10-CM diagnosis codes	Procedures	CPT, DRG, HCPCS, ICD-10-PCS, procedure codes
Lower GI	Prolapse or intussusception	K622, K623, K561	Colectomy	CPT: 44140, 44141, 44143, 44144, 44145, 44146, 44147, 44150, 44151, 44155, 44156, 44157, 44158, 44160, 44204, 44205, 44206, 44207, 44208, 44210, 44211, 44212, 44139, 44213 ICD-10-PCS: 0DTE0ZZ, 0DTE4ZZ, 0DTE7ZZ, 0DTE8ZZ, 0DTF0ZZ, 0DTF4ZZ, 0DTF7ZZ, 0DTF8ZZ, 0DTG0ZZ, 0DTG4ZZ, 0DTG7ZZ, 0DTG8ZZ, 0DTGFZZ, 0DTH0ZZ, 0DTH4ZZ, 0DTH7ZZ, 0DTH8ZZ, 0DTK0ZZ, 0DTK4ZZ, 0DTK7ZZ, 0DTK8ZZ, 0DTL0ZZ, 0DTL4ZZ, 0DTL7ZZ, 0DTL8ZZ, 0DTLFZZ, 0DTM0ZZ, 0DTM4ZZ, 0DTM7ZZ, 0DTM8ZZ, 0DTMFZZ, 0DTN0ZZ, 0DTN4ZZ, 0DTN7ZZ, 0DTN8ZZ, 0DTNFZZ, 0DTC0ZZ, 0DTC4ZZ, 0DTC7ZZ, 0DTC8ZZ, 0DTF4ZG, 0DTG4ZG, 0DTL4ZG, 0DTM4ZG, 0DTN4ZG

DIOS, ileus, fecal impaction or other intestinal obstruction	K5641, K5649, K56600 ,K56601, K56609, K56690, K56691, K56699, K567, E8411, E8419	Small intestine resection	CPT: 44120, 44121, 44125, 44202, 44203, 44227, 44625, 44626 ICD-10-PCS: 0DT80ZZ, 0DT84ZZ, 0DT87ZZ, 0DT88ZZ, 0DTB0ZZ, 0DTB4ZZ, 0DTB7ZZ, 0DTB8ZZ
Constipation	K5900, K5901, K5902, K5903, K5904, K5909	Therapeutic enema	CPT: 74283
Functional diarrhea	K591	Colostomy	CPT: 44141, 44143, 44144, 44146, 44160, 44205, 44206, 44208, 44188, 44320 ICD-10-PCS: 0D1E074 , 0D1E0J4 , 0D1E0K4 , 0D1E0Z4 , 0D1E474 , 0D1E4J4 , 0D1E4K4 , 0D1E4Z4 , 0D1E874 , 0D1E8J4 , 0D1E8K4 , 0D1E8Z4 , 0D1H074 , 0D1H0J4 , 0D1H0K4 , 0D1H0Z4 , 0D1H3J4 , 0D1H474 , 0D1H4J4 , 0D1H4K4 , 0D1H4Z4 , 0D1H874 , 0D1H8J4 , 0D1H8K4 , 0D1H8Z4 , 0D1K074 , 0D1K0J4 , 0D1K0K4 , 0D1K0Z4 , 0D1K3J4 , 0D1K474 , 0D1K4J4 , 0D1K4K4 , 0D1K4Z4
Other intestinal malabsorption (SIBO)	K9089	Ileostomy	CPT: 44187, 44310 ICD-10-PCS: 0D1B074 , 0D1B0J4 , 0D1B0K4 , 0D1B0Z4 , 0D1B3J4 , 0D1B474 , 0D1B4J4 , 0D1B4K4 , 0D1B4Z4 , 0D1B874 , 0D1B8J4 , 0D1B8K4 , 0D1B8Z4

Nutrition	Failure to thrive	R6251, R627	Feeding tube placement	CPT: 43246, 49440, 43760, 43752, 43762, 43763, 43761, 44373, 44372, 49446, 49452, 0647T, 43831, 43832, 44015, 49441, 49451
	Feeding difficulties	R6330, R6331, R6332, R6339		
	Abnormal weight changes	R634, R635		
	Underweight	R636, Z6851, Z681		

Electrolyte	Hyper-/hypokalemia	E875, E876	None	None
	Hyper-/hyponatremia	E870, E871		
	Hyper-/hypoosmolarity	E870, E871		
	Other electrolyte and fluid disorders	E872, E873, E874, E8770, E8779, E878		
	Volume depletion, hypovolemia, dehydration	E860, E861, E869		
CFRD	CFRD with hyperosmolarity	E0800, E0801	None	None
	CFRD with ketoacidosis	E0810, E0811		
	CFRD with hypoglycemia	E08641, E08649		
	CFRD with hyperglycemia	E0865		
	CFRD with foot or other skin ulcer	E08621, E08622		
Hepatobiliary	Cholelithiasis	K8000, K8001, K8010, K8011, K8012, K8013, K8018, K8019, K8020, K8021, K8030, K8031, K8032, K8033, K8034, K8035, K8036, K8037,	Cholecystectomy	CPT: 47562, 47563, 47564, 47600, 47605, 47610, 47612, 47620 DRG: 411, 412, 413, 417, 418, 419

		K8040, K8041, K8042, K8043, K8044, K8045, K8046, K8047, K8050, K8051, K8060, K8061, K8062, K8063, K8064, K8065, K8066, K8067, K8070, K8071, K8080, K8081		ICD-10-PCS: 0FT40ZZ, 0FT44ZZ
	Acute cholecystitis	K8000, K8001, K810, K812, K819, K82A1, K82A2	Liver transplant	CPT: 47135, 47136 HCPSCS: S2053 ICD-10-PCS: 0FY00Z0, 0FY00Z1, 0FY00Z2
	Biliary colic	K8050, K8051		
	Biliary or other cirrhosis	K743, K744, K745, K7460, K7469, K766		
	Ascites (non-malignant)	R188		
	Hepatic failure or hepatic fibrosis	K7200, K7201, K7210, K7211, K7290, K7291, K740		
Upper respiratory	Acute sinusitis	J0100, J0101, J0110, J0111, J0120, J0121, J0130, J0131, J0140, J0141, J0180, J0181, J0190, J0191	Nasal polypectomy	CPT: 30110, 30115
	Nasal cyst or mucocele	J341	Other functional endoscopic sinus surgery	CPT: 31237, 31238, 31240, 31254, 31255, 31256, 31267, 31295, 31296, 31297, 31298, 31241, 31253, 31257, 31259, 31287, 31288, 31292, 31293
	Acute nasopharyngitis,	J00, J069, J09X2, J101, J111, J398	Other nasal surgery (e.g.,	CPT: 30130, 30140, 30801, 30802, 31000, 31002, 31020, 31030, 31032, 31050, 31051, 31070, 31075, 31080, 31081,

	flu without pneumonia		turbinate reduction)	31084, 31085, 31086, 31087, 31090, 31200, 31201, 31205
	Mixed simple and mucopurulent chronic bronchitis	J418		
Upper GI	Esophagitis with bleeding	K2081, K2091	Fundoplication	CPT: 43210, 43280, 43281, 43282, 43279, 43284 ICD-10-PCS: 0DV10ZZ, 0DV14ZZ, 0DV20ZZ, 0DV23ZZ, 0DV40ZZ, 0DV54ZZ
	GERD with bleeding	K2101	Esophagogastroduodenoscopy (EGD) for GERD	CPT: 43210, 43257, 43233, 43249, 43245, 43248
	Gastroparesis	K3184		
	Pancreatitis, excluding alcohol induced	K8530, K8531, K8532, K8580, K8581, K8582, K8590, K8591, K8592, K861		
	Pancreatic cyst or pseudocyst	K862, K863, K869		

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26 CF: cystic fibrosis; CFRD: CF-related diabetes; DIOS: distal intestinal obstruction syndrome; GI: gastrointestinal; GERD:

27 gastroesophageal reflux disease; SIBO: small intestinal bacterial overgrowth.

28 **Table E2.** Extrapulmonary Complications

	Pre-treatment N = 1,612		Post-treatment N = 1,612		Relative change (post- treatment vs. pre- treatment)*	P-value (post- treatment vs. pre- treatment)†
	n	%	n	%		
Any claim for a complication						
Any complication	1,209	75.0%	1,040	64.5%	-14.0%	<0.001
Lower GI	951	59.0%	782	48.5%	-17.8%	<0.001
Nutritional	313	19.4%	225	14.0%	-28.1%	<0.001
Electrolyte	102	6.3%	60	3.7%	-41.2%	<0.001
CFRD	69	4.3%	56	3.5%	-18.8%	0.112
Hepatobiliary	88	5.5%	83	5.1%	-5.7%	0.600
Upper respiratory	442	27.4%	297	18.4%	-32.8%	<0.001
Upper GI	89	5.5%	82	5.1%	-7.9%	0.463
Complication-related inpatient admission						
Any complication	397	24.6%	142	8.8%	-64.2%	<0.001
Lower GI	303	18.8%	99	6.1%	-67.3%	<0.001
Nutritional	79	4.9%	18	1.1%	-77.2%	<0.001
Electrolyte	63	3.9%	38	2.4%	-39.7%	0.008
CFRD	49	3.0%	21	1.3%	-57.1%	<0.001
Hepatobiliary	34	2.1%	22	1.4%	-35.3%	0.077
Upper respiratory	70	4.3%	26	1.6%	-62.9%	<0.001
Upper GI	36	2.2%	13	0.8%	-63.9%	<0.001

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30 CF: cystic fibrosis; CFRD: CF-related diabetes; GI: gastrointestinal; N: total number of patients in the cohort; n: number of patients
 31 with at least one claim for the indicated complication.

32 *Relative change was calculated as change at the post-treatment period from the pre-treatment period (post-treatment - pre-
33 treatment) divided by the pre-treatment value.

34 †p-values calculated using McNemar's test.

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36 **Table E3.** Extrapulmonary Complications by Age at Index

	6–11 Years						≥12 Years					
	Pre-treatment		Post-treatment		Relative change (post-treatment vs. pre-treatment)*	P-value (post-treatment vs. pre-treatment)†	Pre-treatment		Post-treatment		Relative change (post-treatment vs. pre-treatment)*	P-value (post-treatment vs. pre-treatment)†
	N = 321		N = 321				N = 1,291		N = 1,291			
	n	%	n	%	n	%	n	%				
Any claim for a complication												
Any complication	234	72.9%	247	77.0%	5.6%	0.149	975	75.5%	793	61.4%	-18.7%	<0.001
Lower GI	188	58.6%	185	57.6%	-1.6%	0.710	763	59.1%	597	46.2%	-21.8%	<0.001
Nutritional	65	20.3%	71	22.1%	9.2%	0.460	248	19.2%	154	11.9%	-37.9%	<0.001
Electrolyte	<10		<10		NR	NR	94	7.3%	57	4.4%	-39.4%	<0.001
CFRD	<10		<10		NR	NR	66	5.1%	53	4.1%	-19.7%	0.101
Hepatobiliary	<10		<10		NR	NR	83	6.4%	75	5.8%	-9.6%	0.371
Upper respiratory	62	19.3%	93	29.0%	50.0%	0.001	380	29.4%	204	15.8%	-46.3%	<0.001
Upper GI	<10		<10		NR	NR	82	6.4%	76	5.9%	-7.3%	0.502
Complication-related inpatient admission												
Any complication	37	11.5%	16	5.0%	-56.8%	0.001	360	27.9%	126	9.8%	-65.0%	<0.001
Lower GI	28	8.7%	12	3.7%	-57.1%	NR	275	21.3%	87	6.7%	-68.4%	<0.001
Nutritional	10	3.1%	<10		NR	NR	69	5.3%	17	1.3%	-75.4%	<0.001
Electrolyte	<10		<10		NR	NR	59	4.6%	37	2.9%	-37.3%	0.016
CFRD	<10		<10		NR	NR	46	3.6%	20	1.6%	-56.5%	<0.001
Hepatobiliary	<10		<10		NR	NR	34	2.6%	22	1.7%	-35.3%	0.077
Upper respiratory	<10		<10		NR	NR	63	4.9%	22	1.7%	-65.1%	<0.001
Upper GI	<10		<10		NR	NR	35	2.7%	13	1.0%	-62.9%	<0.001

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38 CF: cystic fibrosis; CFRD: CF-related diabetes; GI: gastrointestinal; N: total number of patients in the cohort; n: number of patients

39 with at least one claim for the indicated complication; NR: Not reported.

40 *Relative change was calculated as change at the post-treatment period from the pre-treatment period (post-treatment - pre-
41 treatment) divided by the pre-treatment value.

42 †p-values calculated using McNemar's test.

43 p-values are not reported when both comparator groups have $N < 30$; outcomes for sample sizes $N < 10$ were masked.

44 **Table E4.** Extrapulmonary Complications by Payer

	Commercial						Medicaid					
	Pre-treatment		Post-treatment		Relative change (post-treatment vs. pre-treatment)*	P-value (post-treatment vs. pre-treatment)†	Pre-treatment		Post-treatment		Relative change (post-treatment vs. pre-treatment)*	P-value (post-treatment vs. pre-treatment)†
	N = 864		N = 864				N = 748		N = 748			
	n	%	n	%	n	%	n	%				
Any claim for a complication												
Any complication	631	73.0%	523	60.5%	-17.1%	<0.001	578	77.3%	517	69.1%	-10.6%	<0.001
Lower GI	477	55.2%	381	44.1%	-20.1%	<0.001	474	63.4%	401	53.6%	-15.4%	<0.001
Nutritional	129	14.9%	93	10.8%	-27.9%	0.001	184	24.6%	132	17.7%	-28.3%	0.001
Electrolyte	53	6.1%	27	3.1%	-49.1%	0.001	49	6.6%	33	4.4%	-32.7%	0.001
CFRD	26	3.0%	24	2.8%	-7.7%	NR	43	5.8%	32	4.3%	-25.6%	0.683
Hepatobiliary	49	5.7%	47	5.4%	-4.1%	0.782	39	5.2%	36	4.8%	-7.7%	0.782
Upper respiratory	237	27.4%	152	17.6%	-35.9%	<0.001	205	27.4%	145	19.4%	-29.3%	<0.001
Upper GI	57	6.6%	49	5.7%	-14.0%	0.248	32	4.3%	33	4.4%	3.1%	0.248
Complication-related inpatient admission												
Any complication	175	20.3%	59	6.8%	-66.3%	<0.001	222	29.7%	83	11.1%	-62.6%	<0.001
Lower GI	125	14.5%	43	5.0%	-65.6%	<0.001	178	23.8%	56	7.5%	-68.5%	<0.001
Nutritional	29	3.4%	<10		NR	NR	50	6.7%	14	1.9%	-72.0%	<0.001
Electrolyte	31	3.6%	18	2.1%	-41.9%	0.042	32	4.3%	20	2.7%	-37.5%	0.042
CFRD	17	2.0%	<10		NR	NR	32	4.3%	16	2.1%	-50.0%	0.001
Hepatobiliary	16	1.9%	12	1.4%	-25.0%	NR	18	2.4%	10	1.3%	-44.4%	NR
Upper respiratory	34	3.9%	<10		NR	NR	36	4.8%	17	2.3%	-52.8%	<0.001
Upper GI	25	2.9%	<10		NR	NR	11	1.5%	<10		NR	NR

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46 CF: cystic fibrosis; CFRD: CF-related diabetes; GI: gastrointestinal; N: total number of patients in the cohort; n: number of patients

47 with at least one claim for the indicated complication; NR: Not reported.

48 *Relative change was calculated as change at the post-treatment period from the pre-treatment period (post-treatment - pre-
49 treatment) divided by the pre-treatment value.

50 †p-values calculated using McNemar's test.

51 p-values are not reported when both comparator groups have $N < 30$; outcomes for sample sizes $N < 10$ were masked.

52 **Table E5.** Extrapulmonary Complications by CFTRm Experience

	CFTRm Naïve						CFTRm Experienced					
	Pre-treatment		Post-treatment		Relative change (post-treatment vs. pre-treatment)*	P-value (post-treatment vs. pre-treatment)†	Pre-treatment		Post-treatment		Relative change (post-treatment vs. pre-treatment)*	P-value (post-treatment vs. pre-treatment)†
	N = 697		N = 697				N = 915		N = 915			
	n	%	n	%			n	%	n	%		
Any claim for a complication												
Any complication	527	75.6%	456	65.4%	-13.5%	<0.001	682	74.5%	584	63.8%	-14.4%	<0.001
Lower GI	398	57.1%	333	47.8%	-16.3%	<0.001	553	60.4%	449	49.1%	-18.8%	<0.001
Nutritional	155	22.2%	103	14.8%	-33.5%	<0.001	158	17.3%	122	13.3%	-22.8%	0.002
Electrolyte	45	6.5%	30	4.3%	-33.3%	0.051	57	6.2%	30	3.3%	-47.4%	0.002
CFRD	34	4.9%	28	4.0%	-17.6%	0.289	35	3.8%	28	3.1%	-20.0%	0.237
Hepatobiliary	48	6.9%	50	7.2%	4.2%	0.777	40	4.4%	33	3.6%	-17.5%	0.274
Upper respiratory	183	26.3%	126	18.1%	-31.1%	<0.001	259	28.3%	171	18.7%	-34.0%	<0.001
Upper GI	43	6.2%	41	5.9%	-4.7%	0.763	46	5.0%	41	4.5%	-10.9%	0.466
Complication-related inpatient admission												
Any complication	191	27.4%	66	9.5%	-65.4%	<0.001	206	22.5%	76	8.3%	-63.1%	<0.001
Lower GI	149	21.4%	44	6.3%	-70.5%	<0.001	154	16.8%	55	6.0%	-64.3%	<0.001
Nutritional	46	6.6%	<10		NR	NR	33	3.6%	<10		NR	NR
Electrolyte	26	3.7%	21	3.0%	-19.2%	NR	37	4.0%	17	1.9%	-54.1%	0.006
CFRD	27	3.9%	12	1.7%	-55.6%	NR	22	2.4%	<10	1.0%	NR	NR
Hepatobiliary	20	2.9%	14	2.0%	-30.0%	NR	14	1.5%	<10		NR	NR
Upper respiratory	27	3.9%	11	1.6%	-59.3%	NR	43	4.7%	15	1.6%	-65.1%	<0.001
Upper GI	19	2.7%	<10		NR	NR	17	1.9%	<10		NR	NR

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54 CF: cystic fibrosis; CFRD: CF-related diabetes; GI: gastrointestinal; N: total number of patients in the cohort; n: number of patients

55 with at least one claim for the indicated complication; NR: Not reported.

56 *Relative change was calculated as change at the post-treatment period from the pre-treatment period (post-treatment - pre-
57 treatment) divided by the pre-treatment value.

58 †p-values calculated using McNemar's test.

59 p-values are not reported when both comparator groups have $N < 30$; outcomes for sample sizes $N < 10$ were masked.

60 **Table E6.** Extrapulmonary Complications in 3-year Post-treatment Sample

	Pre-Treatment Period		Year-1 Post-Treatment				Year-2 Post-Treatment				Year-3 Post-Treatment			
	N = 206		N = 206		Relative change (post-treatment vs. pre-treatment)*	P-value (post-treatment vs. pre-treatment)†	N = 206		Relative change (post-treatment vs. pre-treatment)*	P-value (post-treatment vs. pre-treatment)†	N = 206		Relative change (post-treatment vs. pre-treatment)*	P-value (post-treatment vs. pre-treatment)†
	n	%	n	%			n	%			n	%		
Medical claim in any site of care, any complication	158	77%	124	60.2%	-21.5%	<0.001	114	55.3%	-27.8%	<0.001	109	52.9%	-31.0%	<0.001
Inpatient admissions, any complication	65	32%	15	7.3%	-76.9%	<0.001	17	8.3%	-73.8%	<0.001	14	6.8%	-78.5%	<0.001

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62 N: total number of patients in the cohort; n: number of patients with at least one claim for the indicated complication.

63 *Relative change was calculated as change at the post-treatment period from the pre-treatment period (post-treatment - pre-
64 treatment) divided by the pre-treatment value.

65 †p-values calculated using McNemar's test.

66