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Correction

Correction: Dagenais et al. Real-World Safety of CFTR Modulators in the Treatment of Cystic Fibrosis: A Systematic Review. *J. Clin. Med.* 2021, *10*, 23

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In the original article [1], there was a mistake in Table 1 as published. Reference citation [34] was wrong. The corrected Table 1 appears below. The authors state that the scientific conclusions are unaffected. The original article has been updated.

In the original article [1], there was a mistake in Table 2 as published. Subtitle "Lumacaftor/Ivacaftor" was wrong. The corrected Table 2 appears below. The authors state that the scientific conclusions are unaffected. The original article has been updated.

In the original article [1], there was a mistake in Table A2 as published. Reference citation [48,49,53,54] were wrong. "Talkwalker" was misspelled. The corrected Table A2 appears below. The authors state that the scientific conclusions are unaffected. The original article has been updated.

Citation: Dagenais, R.V.E.; Su, V.C.; Quon, B.S. Correction: Dagenais et al. Real-World Safety of CFTR Modulators in the Treatment of Cystic Fibrosis: A Systematic Review. *J. Clin. Med.* 2021, *10*, 23. *J. Clin. Med.* **2022**, *11*, 318. https://doi.org/10.3390/jcm11020318

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Table 1. Summary of characteristics and results of cohort or survey studies with full manuscript.

Ref	Study Design & Location	Population [a]	*n*	Recruitment Period & Follow-Up Duration	Overall Adverse Events (AE) [b,c]			Dose Modification, Interruption, or Discontinuation Due to AE [b,c]		
Ivacaftor										
[29]	Prospective Cohort [d] United States	**Baseline Age** Pediatric and Adult - Mean: 33 yr - Range: 10–61 yr **CFTR Genotype** ≥1 copy G551D **Baseline ppFEV$_1$** Mean: 30%	44	**Recruitment Period** Prior to commercial availability **Follow-Up Duration** NS	**AE in *n* = 38 (86%):** - Pulmonary exacerbation - Hemoptysis - Increased sputum - Increased cough - URTI - Dyspnea - Abnormal respiration - Respiratory tract congestion - Headache - Rash **SAE in *n* = 14 (32%):** - Pulmonary exacerbation - Hemoptysis - Pneumothorax - Acute respiratory failure - URTI - Abdominal pain - Gastroenteritis - Abnormal LFTs - Syncope - Secondary adrenocortical insufficiency	*n* 20 7 7 6 6 3 3 3 5 4 NS NS NS NS NS NS NS NS NS NS	% 45 16 16 14 14 7 7 7 11 9 - - - - - - - - - -	**Discontinuation:** - Severe abdominal pain - Dizziness/tinnitus	*n* 1 1	% 2 2

Table 1. *Cont.*

Ref	Study Design & Location	Population [a]	*n*	Recruitment Period & Follow-Up Duration	Overall Adverse Events (AE) [b,c]			Dose Modification, Interruption, or Discontinuation Due to AE [b,c]
[55]	Prospective Cohort United States Canada Italy	**Baseline Age** Pediatric and Adult - Mean: 17 yr - Range: 5–61 yr **CFTR Genotype** ≥1 gating mutation **Baseline ppFEV$_1$** Mean: 86%	23	**Recruitment Period** Mar 2014 to Aug 2015 **Follow-Up Duration** 3 mo	**49 AE in *n* = 21 (91%):** - Respiratory, unspecified - Gastrointestinal, unspecified - Infection, unspecified - Headache - Weakness - Dizziness - Fatigue **5 SAE in *n* = 3 (13%):** - Respiratory infection - Acute changes in metabolic and liver status	*n* NS NS NS NS NS NS NS *n* 4 1	% - - - - - - - % 17 4	None reported
[56]	Retrospective Cohort United Kingdom (1 center)	**Baseline Age** Pediatric - Mean: 9 yr - Range: 6–14 yr **CFTR Genotype** 1 copy G551D **Baseline ppFEV$_1$** Mean: 68% [e]	4	**Recruitment Period** Jan 2013 to Jun 2015 **Follow-Up Duration** Mean: 24 mo	- Transaminitis (<3 x ULN)	*n* 1	% 25	None reported
[57]	Retrospective Cohort Scotland (11 centers)	**Baseline Age** Pediatric - Median: 9 yr **CFTR Genotype** ≥1 copy G551D **Baseline ppFEV$_1$** Mean: 85%	26	**Recruitment Period** NS (Jan 2013 to Mar 2013 for 85%) **Follow-Up Duration** Mean: 17 mo	- Headache - Swollen ear - Cataracts	*n* 1 1 2	% 4 4 17 [f]	None reported

Table 1. *Cont.*

Ref	Study Design & Location	Population [a]	*n*	Recruitment Period & Follow-Up Duration	Overall Adverse Events (AE) [b,c]			Dose Modification, Interruption, or Discontinuation Due to AE [b,c]		
[58]	Retrospective Cohort France (25 centers)	**Baseline Age** Pediatric and Adult - Median: 18 yr - Range: 6–52 yr **CFTR Genotype** ≥1 copy G551D **Baseline ppFEV$_1$** Mean: 72%	57	**Recruitment Period** Pre-1 Jun 2013 up to 30 Sep 2014 **Follow-Up Duration** Up to 2 yr	**34 AE in *n* = 21 (37%):** - Transaminitis - Rhinopharyngitis - Asthma - Fever - Chest pain - Abdominal pain - Nausea or vomiting - Intestinal dysmotility - Headache - Fatigue - Rash or eczema - Depression - Myalgia - Arthritis - Breast hypertrophy - Orchitis - Atrial fibrillation	*n* 3 NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS	% 5 - - - - - - - - - - - - - - - -	**Interruption in *n* = 7 (12%):** - Hepatitis - Rhinopharyngitis - Abdominal pain - Vomiting - Headache - Rash - Severe depression **Discontinuation:** - Transaminitis - Liver cirrhosis diagnosis	*n* NS NS NS NS NS NS NS 1 1	% - - - - - - - 2 2
[30]	Retrospective Cohort [d] Germany (multicenter)	**Baseline Age** Adult - Mean: 34 yr **CFTR Genotype** ≥1 copy G551D **Baseline ppFEV$_1$** Mean: 25%	14	**Recruitment Period** Sep 2012 to Apr 2013 **Follow-Up Duration** Mean: 235 days	- Increased bronchial and nasal secretions - Headache - Worsening RLS - Abdominal pain - Hyperbilirubinemia (mild) - Transaminitis (<3 to 4x ULN)	*n* 3 1 1 1 1 1	% 21 7 7 7 7 7	**Discontinuation:** - Increased bronchial and nasal secretions * * Trial of reduced dose before discontinuation	*n* 1	% 7
Lumacaftor/Ivacaftor										
[41]	Prospective Cohort France (1 center)	**Baseline Age** Pediatric - Mean: 16 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 87%	32	**Recruitment Period** Mar 2016 to Dec 2016 **Follow-Up Duration** 4 h post-first dose	- Acute drop in ppFEV$_1$ - Wheeze	*n* 32 3	% 100 9	None reported		

Table 1. *Cont.*

Ref	Study Design & Location	Population [a]	*n*	Recruitment Period & Follow-Up Duration	Overall Adverse Events (AE) [b,c]			Dose Modification, Interruption, or Discontinuation Due to AE [b,c]		
[42]	Prospective Cohort France (47 centers)	**Baseline Age** Pediatric and Adult - Mean: 22 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 65%	845	**Recruitment Period** 1 Jan 2016 to 31 Dec 2016 **Follow-Up Duration** 12 mo	**AE in *n* = 494 (59%):** - Respiratory - Digestive - Menstrual abnormality - Fatigue - Headache - CK > 5xULN - Transaminitis (> 3xULN)	*n* 316 181 53 37 19 20 5	% 37 21 6 4 2 2 0.6	**Interruption:** - Respiratory - 'Non-respiratory' **Discontinuation:** Respiratory - Chest tightness/dyspnea - Bronchospasm - Increased cough/sputum - Hemoptysis - Pneumothorax Non-respiratory - Diarrhea, abdominal pain - CK >10xULN + myalgia - Fatigue - Headache - Depression - Metrorrhagia - Transaminitis (>6xULN) - Cutaneous rash - Tachycardia	*n* 16 8 *n* 38 24 9 2 1 18 5 5 4 4 3 2 1 1	% 2 1 % 5 3 1 0.2 0.1 2 0.6 0.6 0.5 0.5 0.4 0.2 0.1 0.1
[59]	Prospective Cohort United States (1 center)	**Baseline Age** Pediatric and Adult - Mean: 23 yr - Range: 12–48 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 70%	26	**Recruitment Period** NS **Follow-Up Duration** 6 mo	See **Discontinuation**			**Discontinuation:** - Transaminitis - Unspecified AE	*n* 1 4	% 4 15

Table 1. *Cont.*

Ref	Study Design & Location	Population [a]	*n*	Recruitment Period & Follow-Up Duration	Overall Adverse Events (AE) [b,c]			Dose Modification, Interruption, or Discontinuation Due to AE [b,c]		
						n	%		*n*	%
[31]	Prospective Cohort [d] Switzerland (1 center)	**Baseline Age** Adult - Mean NR **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Median: 30%	20	**Recruitment Period** Jan 2016 to Jan 2017 **Follow-Up Duration** 1 mo	- Dyspnea			**Reduced dose:**		
					- 3 h	0	-	- Respiratory intolerance	3	15
					- 24 h	1	5			
					- 1 mo	1	5	**Discontinuation:**		
					- Chest tightness			- Chest tightness (at 24 h)	1	5
					- 3 h	1	5			
					- 24 h	10	50			
					- 1 mo	1	5			
					- Increased sputum					
					- 3 h	1	5			
					- 24 h	8	40			
					- 1 mo	3	15			
					- Pulmonary exacerbation					
					- 1 mo	2	10			
[32]	Prospective Cohort Australia (1 center)	**Baseline Age** Adult - Mean: 27 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Median: 36%	12	**Recruitment Period** Jan 2016 to Oct 2016 **Follow-Up Duration** 1 mo		*n*	%	**Discontinuation:**	*n*	%
					- Acute drop in ppFEV$_1$	12	100	- Chest tightness/dyspnea *	3	25
					- Respiratory AE overall					
					- 4 h	5	42	* *n* = 2 discontinued after 1mo follow-up (5 wk and 9 wk)		
					- 24 h	10	83			
					- 1 mo	8	67			
					- Dyspnea					
					- 4 h	2	17			
					- 24 h	6	50			
					- 1 mo	7	58			
					- Chest tightness					
					- 4 h	4	33			
					- 24 h	8	67			
					- 1 mo	5	42			
					- Increased sputum					
					- 4 h	0	-			
					- 24 h	2	17			
					- 1 mo	1	8			
					- Pulmonary exacerbation	6	50			

Table 1. *Cont.*

Ref	Study Design & Location	Population [a]	*n*	Recruitment Period & Follow-Up Duration	Overall Adverse Events (AE) [b,c]			Dose Modification, Interruption, or Discontinuation Due to AE [b,c]		
[33]	Prospective Cohort France (11 centers)	**Baseline Age** Adult - Mean: 31 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 32%	53	**Recruitment Period** Jan 2016 to Jun 2016 **Follow-Up Duration** 3 mo	**AE in *n* = 34 (63%)**: - Abnormal respiration - Dyspnea - Increased cough - Abdominal pain, nausea, diarrhea, or vomiting - Fatigue - Rash - Pruritus - Breast tension	*n* 13 11 3 9 2 1 1 1	% 25 21 6 17 4 2 2 2	**Discontinuation:** - Respiratory intolerance - Vomiting - Fatigue	*n* 13 1 1	% 25 2 2
[25]	Prospective Cohort [d,g] Australia (1 center)	**Baseline Age** Adult - Mean: 27 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 36%	10	**Recruitment Period** NS **Follow-Up Duration** 52 wk	**AE in *n* = 6 (60%):** - Chest tightness/dyspnea - Headache	*n* 6 2	% 60 20	None reported		
[43]	Retrospective Cohort Ireland (1 center)	**Baseline Age** Pediatric - Mean: 14 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 77%	15	**Recruitment Period** Sep 2016 to Aug 2017 **Follow-Up Duration** NS	- Acute drop in ppFEV$_1$ - Chest tightness - Increased sputum	*n* 14 2 2	% 93 13 13	None reported		

Table 1. *Cont.*

Ref	Study Design & Location	Population [a]	*n*	Recruitment Period & Follow-Up Duration	Overall Adverse Events (AE) [b,c]			Dose Modification, Interruption, or Discontinuation Due to AE [b,c]		
[44]	Retrospective Cohort United States (1 center)	**Baseline Age** Pediatric and Adult - Mean: 25 yr - Range: 12–59 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 67%	116	**Recruitment Period** NS **Follow-Up Duration** Up to 11 mo	**AE in *n* = 46 (40%):** - Chest tightness - Dyspnea - Increased cough - Diarrhea - Nausea - Decreased appetite - Rash	*n* 23 12 10 5 3 2 2	% 20 10 9 4 3 2 2	**Reduced dose:** - AE not specified **Discontinuation:** - Reasons not specified [h]	*n* 10 20	% 9 17
[60]	Retrospective Cohort Greece (1 center)	**Baseline Age** Pediatric and Adult - Mean: 16 yr [i] - Range: 12–23 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean 92% [i]	62	**Recruitment Period** Mar 2016 to Aug 2017 **Follow-Up Duration** 12 mo	- Chest tightness	*n* 2	% 3	**Discontinuation:** - Transaminitis - Cataract	*n* 1 1	% 2 2
[34]	Retrospective Cohort [d] Spain (multicenter)	**Baseline Age** Pediatric and Adult - Mean: 27 yr - Range: 10–45 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 32%	20	**Recruitment Period** 2016 **Follow-Up Duration** 6 mo	**AE in *n* = 15 (75%):** - Chest tightness - Dyspnea - Headache - Weight loss - 'Sickness' (not defined) - Asthenia - Abdominal pain - Transaminitis	*n* 9 8 5 5 3 3 2 2	% 45 40 25 25 15 15 10 10	**Discontinuation:** - Decreased ppFEV$_1$ - AE not specified	*n* 1 6	% 5 30

Table 1. *Cont.*

Ref	Study Design & Location	Population [a]	*n*	Recruitment Period & Follow-Up Duration	Overall Adverse Events (AE) [b,c]			Dose Modification, Interruption, or Discontinuation Due to AE [b,c]		

[45]	Retrospective Cohort
	
	Canada
	(1 center)
		Baseline Age
		Adult
		- Median: 32 yr
		
		CFTR Genotype
		ΔF508/ΔF508
		
		Baseline ppFEV$_1$
		Median: 40%
			22	**Recruitment Period**
				Apr 2016 to Jun 2018
				
				Follow-Up Duration
				Median: 10 mo
					AE in *n* = 19 (86%):
					- Chest tightness
					- Wheeze
					- Dyspnea
					- Increased sputum
					- Increased cough
					- Flu-like symptoms
					- Elevated blood pressure
					- Headache
					- Nausea
					- Elevated AST
					- Anxiety
					- Bradycardia
					- Pleuritic chest pain
						n
						14
						4
						3
						3
						2
						1
						5
						4
						2
						1
						1
						1
						1
							%
							64
							18
							14
							14
							9
							5
							23
							18
							9
							5
							5
							5
							5
								Discontinuation:
								- Respiratory symptoms
								- Asymptomatic hypertension
								- Symptomatic hypertension
								  - Headache
								  - Hypertensive emergency
								- Anxiety
									n
									3
									2
									
									1
									1
									1
										%
										14
										9
										
										5
										5
										5

[61]	Retrospective Cohort United States (1 center)	**Baseline Age** Adult - Mean NR **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	82	**Recruitment Period** Jul 2015 to Jun 2016 **Follow-Up Duration** 12 mo	See **Discontinuation**			**Discontinuation:** Total overall: - Chest tightness * - Diarrhea ** - Abdominal pain - Nausea ** - Dysphagia - Elevated LFTs - Pericarditis - Allergic reaction ** - Suspected Stevens–Johnson syndrome * *n* = 3 also had significant drop in ppFEV$_1$ ** *n* = 1 also discontinued due to chest tightness	*n* 17 11 2 1 1 1 1 1 1 1	% 21 13 2 1 1 1 1 1 1 1

Table 1. *Cont.*

Ref	Study Design & Location	Population [a]	*n*	Recruitment Period & Follow-Up Duration	Overall Adverse Events (AE) [b,c]			Dose Modification, Interruption, or Discontinuation Due to AE [b,c]		
[26]	Retrospective Cohort [d,g] Australia (7 centers)	**Baseline Age** Adult - Mean: 31 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 37%	72	**Recruitment Period** Nov 2015 to Mar 2017 **Follow-Up Duration** 12 mo		*n*	%	**Discontinuation:**	*n*	%
					- Chest tightness/dyspnea	40	56	- Chest tightness/dyspnea	22	31
					- Increased sputum	4	6			
					- Decrease in ppFEV$_1$	2	3			
					- Headache	2	3			
					- Fatigue	5	7			
					- Nausea	1	1			
					- Rash	2	3			
[27]	Case Series (Survey) [j] International (31 centers)	**Baseline Age** Adult - Mean: 30 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 59%	26	**Recruitment Period** Questionnaire sent in 2018–2019 **Follow-Up Duration** NS		*n*	%	**Discontinuation:**	*n*	%
					- Pulmonary exacerbation	1	4	- Chest tightness	2	8
					- Post-partum acute myelocytic leukemia	1	4			

[a] When adult and pediatric patients both included, age range reported when possible; [b] Rates not reported for all AE, as indicated by 'NS'; [c] To avoid redundancy, if AE only reported in context of dose modification, interruption, and/or discontinuation of therapy, it was not listed in overall AE; [d] Study population part of a compassionate, 'expanded access', 'managed access', or 'named patient' program; [e] Mean calculated from $n = 3$ (75%) of study subjects, as baseline not reported for $n = 1$ (25%); [f] Frequency of 17% based on $n = 12$ screened; 8% frequency for overall cohort of $n = 26$; [g] Study was case-control, but only LUM/IVA-treated participants included in systematic review; therefore, assessed as cohort study; [h] Reason for discontinuation was not consistently assessed, and may include reasons unrelated to AE; [i] Mean baseline age and ppFEV$_1$ based on $n = 52$ in final analysis of outcomes assessing effectiveness; $n = 10$ excluded from this analysis; [j] This case series is included in Table 1 due to results being presented in aggregate. **AST**, aspartate aminotransferase; **CFTR**, cystic fibrosis transmembrane conductance regulator; **CK**, creatine kinase; **h**, hour(s); **LFT**, liver function test; **mo**, month(s); **NR**, not reported; **NS**, not specified; **ppFEV$_1$**, percent predicted Forced Expiratory Volume in 1 sec; **RLS**, restless leg syndrome; **SAE**, serious adverse events; **ULN**, upper limit of normal; **URTI**, upper respiratory tract infection; **wk**, week(s); **yr**, year(s).

Table 2. Summary of characteristics and results of cohort or survey studies in abstract form.

Ref	Study Design	Population	*n*	Overall Adverse Events (AE) [a,b]			Dose Modification, Interruption, or Discontinuation Due to AE [a,b]
Ivacaftor							
[62]	Prospective Cohort	**Baseline Age** Pediatric - Mean: 5 yr **CFTR Genotype** ≥1 gating mutation **Baseline ppFEV$_1$** Mean NR	4	**AE in *n* = 2 (50%):** - URTI - Nasal congestion - Headache	*n* NS NS NS	% - - -	None reported
[63]	Retrospective Cohort	**Baseline Age** Pediatric - Mean: 6 yr **CFTR Genotype** ≥1 gating mutation **Baseline ppFEV$_1$** Median: 87%	10	- Transient rash - Increased obesity	*n* 2 1	% 20 10	None reported
[64]	Prospective Cohort	**Baseline Age** Pediatric and Adult - Mean NR **CFTR Genotype** ≥1 copy S549R **Baseline ppFEV$_1$** Mean: 54%	15	- Liver enzyme derangement	*n* 2	% 13	None reported
[65]	Cross-sectional Survey	**Baseline Age** Adult - Mean: 26 yr **CFTR Genotype** ≥1G551D **Baseline ppFEV$_1$** Mean: 62%	11 [d]	**AE in *n* = 8 (73%) [d]:** - Transient rash - Dizziness - Unspecified AE	*n* NS NS NS	% - - -	None reported

Table 2. *Cont.*

Ref	Study Design	Population	*n*	Overall Adverse Events (AE) [a,b]			Dose Modification, Interruption, or Discontinuation Due to AE [a,b]		
Lumacaftor/Ivacaftor									
[66]	Prospective Cohort	**Baseline Age** Pediatric - Mean: 13 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 91%	14		<u>*n*</u>	<u>%</u>	**<u>Reduced dose</u> *:**	<u>*n*</u>	<u>%</u>
				- Acute drop in ppFEV$_1$ (asymptomatic)	1	7	- Chest tightness, tachypnea	1	7
				- Chest tightness, tachypnea (requiring oxygen)	1	7	* Eventual titration to full dose		
[67]	Prospective Cohort	**Baseline Age** Pediatric - Mean: 14 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 87%	13		<u>*n*</u>	<u>%</u>	None reported		
				- Drop in ppFEV$_1$ requiring salbutamol	7	54			
[68]	Prospective Cohort	**Baseline Age** Pediatric and Adult - Mean: 23 yr [e] **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean 61% [e]	369		<u>*n*</u>	<u>%</u>	**<u>Discontinuation</u>**:	<u>*n*</u>	<u>%</u>
				- Bronchospasm	15	4	- Unspecified AE	16	4
				- Dyspnea	12	3			
				- Abnormal respiration	7	2			
				- Unspecified respiratory AE	4	1			
				- Unspecified AE	120	33			
[69]	Prospective Cohort	**Baseline Age** Pediatric and Adult - Mean: 25 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	311	**<u>379 AE in *n* = 213 (68%)</u>:**	n [f]	<u>%</u>	**Interruption (stop/restart)**:	<u>*n*</u>	<u>%</u>
				- Dyspnea	NS	31	- Unspecified AE and other reasons [g]	12	4
				- Cough	NS	6	**<u>Discontinuation</u>**:		
				- GI discomfort (e.g., diarrhea, nausea, abdominal pain)	NS	31	- Unspecified AE and other reasons [g]	42	14
				- Headache	NS	6			
				- Fatigue	NS	5			
				- Unspecified	NS	NR			

Table 2. *Cont.*

Ref	Study Design	Population	*n*	Overall Adverse Events (AE) [a,b]			Dose Modification, Interruption, or Discontinuation Due to AE [a,b]		
[35]	Prospective Cohort [c]	**Baseline Age** Adult - Median: 31 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Median: 28%	14		*n* 7 1	% 50 7	**Discontinuation**: - Respiratory AE and/or rash	*n* 4	% 29
[70]	Prospective Cohort	**Baseline Age** Adult - Mean NR **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	29	- Chest tightness * * *n* = 4 cases severe, requiring hospitalization for IV steroids and antibiotics	*n* 13	% 45	**Reduced dose**: - Chest tightness **Discontinuation**: - Chest tightness	*n* 2 5	% 7 17
[36]	Prospective Cohort [c]	**Baseline Age** Mean NR [h] **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	32	**AE in 88%**: - Respiratory AE - Drop in ppFEV$_1$	n [f] NS NS	% 87 -	**Interruption (stop/restart)**: - Unspecified AEA **Discontinuation**: - Unspecified AE	*n* 1 8	% 3 25
[71]	Retrospective Cohort	**Baseline Age** Pediatric and Adult - Mean NR **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	34	**AE in *n* = 29 (85%):** - Pulmonary exacerbation - Chest tightness - Dyspnea - Diarrhea - Abdominal pain **Serious AE in *n* = 8 (24%)**: - Respiratory failure [i] - Unspecified AE	*n* 16 9 3 3 3 1 7	% 47 26 9 9 9 3 21	**Discontinuation**: - Unspecified AE	*n* 10	% 29

Table 2. *Cont.*

Ref	Study Design	Population	*n*	Overall Adverse Events (AE) [a,b]			Dose Modification, Interruption, or Discontinuation Due to AE [a,b]		
[72]	Retrospective Cohort	**Baseline Age** Pediatric and Adult - Mean: 26 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 68%	103	See **Discontinuation**			**Interruption/discontinuation** [j]: - Chest tightness and/or pain - Elevated LFTs	*n* 17 NS	% 17 -
[73]	Retrospective Cohort	**Baseline Age** Adult - Mean: 31 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 50%	71	**AE in *n* = 41 (58%):** - Chest tightness - Dyspnea - Increased cough - GI (pain, constipation, or diarrhea) - Rash - Pruritus - Irregular menses or metrorrhagia - Breast tension - Headache - Myalgia	*n* 22 8 4 6 4 1 3 2 1 1	% 31 11 6 9 6 1 4 3 1 1	**Discontinuation**: - Dyspnea - Chest tightness - Increased cough - Fatigue	*n* 7 6 3 1	% 10 9 4 1
[74]	Retrospective Cohort	**Baseline Age** Mean NR [h] **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	54	**See Discontinuation**			**Discontinuation**: - Chest tightness, dyspnea, and/or drop in ppFEV$_1$	*n* 8	% 15

Table 2. *Cont.*

Ref	Study Design	Population	*n*	Overall Adverse Events (AE) [a,b]			Dose Modification, Interruption, or Discontinuation Due to AE [a,b]		
[75]	Retrospective Cohort	**Baseline Age** Adult - Mean: 31 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	28		n	%	**Discontinuation**	n	%
				- Increased work of breathing or chest tightness	12	43	- Respiratory intolerance vs. pulmonary exacerbation	1	4
				- Drop in ppFEV$_1$	5	18	- Persistent respiratory intolerance/chest tightness	3	11
							- Rash and swelling of face	1	4
							- Increased anxiety	1	4
[76]	Retrospective Cohort	**Baseline Age** Adult - Mean NR **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	46		n	%	**Discontinuation**:	n	%
				- Drop in ppFEV$_1$	21	46	- Dyspnea, cough, CFPEx, and/or chest tightness	4	9
				- Transaminitis	2	4	- Transaminitis	1	2
							- Headache	NS	-
							- Muscle ache	NS	-
							- Fatigue	NS	-
							- Rash	NS	-
[77]	Retrospective Cohort	**Baseline Age** Adult - Mean NR **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	28	See **Discontinuation**			**Discontinuation**:	n	%
							- SOB and/or drop in ppFEV$_1$	15	54
[78]	Retrospective Cohort	**Baseline Age** Mean: 32 yr [h] **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 62%	20	**Overall AE**:	n	%	**Interruption (stop/restart):**	n	%
				- Chest tightness	NS	-	- Unspecified AE		
				- Elevated LFTs	NS	-	- full-dose restart	2	10
				- Upset stomach	NS	-	- half-dose restart	4	20
				- Increased stool output	NS	-			
				- Rash	NS	-	**Discontinuation**:		
				- Elevated thyroid function test	NS	-	- Unspecified AE	2	10
				- RA exacerbation	NS	-			

Table 2. *Cont.*

Ref	Study Design	Population	*n*	Overall Adverse Events (AE) [a,b]			Dose Modification, Interruption, or Discontinuation Due to AE [a,b]		
[79]	Retrospective Cohort	**Baseline Age** Mean NR [h] **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	60		<u>*n*</u>	<u>%</u>	None reported		
				- Heartburn/reflux	20	33			
				- Abdominal pain	19	32			
				- Loose/oily stools	17	28			
[80]	Retrospective Cohort	**Baseline Age** Mean: 29 yr [h,k] **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 80% [k]	34	See **Discontinuation**			<u>**Discontinuation**</u>:	<u>*n*</u>	<u>%</u>
							Overall total:	11	32
							- Respiratory AE (70%) [f]	NS	-
							- Unspecified reasons [g]	NS	-
[81]	Cohort [l]	**Baseline Age** Pediatric - Mean NR **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	39		<u>*n*</u>	<u>%</u>	None reported		
				- AST >3x ULN	2	5			
[82]	Cohort [l]	**Baseline Age** Pediatric and Adult - Range: 13–48 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	47	**See Discontinuation**			<u>**Discontinuation**</u>: - Thoracic oppression and unspecified AE	<u>*n*</u> 4	<u>%</u> 9

Table 2. *Cont.*

Ref	Study Design	Population	*n*	Overall Adverse Events (AE) [a,b]			Dose Modification, Interruption, or Discontinuation Due to AE [a,b]		
[83]	Cohort [l]	**Baseline Age** Adult - Mean: 28 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 61%	46	See **Discontinuation**			**Discontinuation**: - Dyspnea, increased sputum, and unspecified AE	*n* 6	% 13
[37]	Cohort [c,l]	**Baseline Age** Adult - Mean: 31 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 28%	30		*n*	%	**Discontinuation**: - Respiratory AE, unspecified - Hypertension	*n* 3 1	% 10 3
				- Drop in ppFEV$_1$	30 *	97			
				- Dyspnea, chest tightness, or chest pain	25 *	81			
				- Increased sputum	NS	-			
				*Based on 31 trials of LUM/IVA in 30 patients					
[84]	Cohort [l]	**Baseline Age** Adult - Mean: 31yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 40%	8	See **Interruption**			**Interruption in *n* = 1 (13%)**: - Drop in ppFEV$_1$ - Eczema	*n* 1 1	% 13 13
[38]	Cohort [c,l]	**Baseline Age** Mean NR [h] **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	19	See **Discontinuation**			**Discontinuation**: - Chest tightness and dyspnea	*n* 4	% 21

Table 2. *Cont.*

Ref	Study Design	Population	*n*	Overall Adverse Events (AE) [a,b]			Dose Modification, Interruption, or Discontinuation Due to AE [a,b]		
[85]	Cross-sectional questionnaire	**Baseline Age** Mean NR [h] **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	11	**AE in *n* = 5 (46%)**: - Increased cough - Chest pain - Trouble breathing - Chest tightness - Stomach pain	*n* 4 2 2 1 1	% 36 18 18 9 9	**Discontinuation**: - Increased cough	*n* 1	% 9
Tezacaftor/Ivacaftor									
[86]	Prospective Cohort	**Baseline Age** Pediatric - Mean: 16 yr **CFTR Genotype** ΔF508 homozygous or heterozygous **Baseline ppFEV$_1$** Mean: 82%	72	See **Discontinuation**			**Discontinuation**: Overall total: - New-onset hemoptysis - Persistent nausea/vomiting - Elevated LFTs - Mental health changes - Alterations in blood glucose - Acholic stools	*n* 8 NS NS NS NS NS NS	% 11 - - - - - -
[87]	Prospective Cohort	**Baseline Age** Mean NR [h] **CFTR Genotype** NR **Baseline ppFEV$_1$** Mean NR	50	- AE not specified	*n* 5	% 10	**Discontinuation**: - Liver function abnormalities	*n* 1	% 2
[88]	Prospective Cohort	**Baseline Age** Adult - Mean: 34 yr **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean: 51%	5 [m]	**AE in *n* = 5 (11%)** [m]: - Sleep pattern disturbance - Out of body experience - Visual hallucination - Depersonalization - "Brain fog" - Severe migraine	*n* 2 1 1 1 1 1	% [m] 5 2 2 2 2 2	**Discontinuation**: - Out of body experience, visual hallucination - Depersonalization, "brain fog" - Severe migraine	*n* 1 1 1	% [m] 2 2 2

Table 2. *Cont.*

Ref	Study Design	Population	*n*	Overall Adverse Events (AE) [a,b]			Dose Modification, Interruption, or Discontinuation Due to AE [a,b]		
[89]	Retrospective Cohort	**Baseline Age** Adult - Mean NR **CFTR Genotype** ΔF508/ΔF508 **Baseline ppFEV$_1$** Mean NR	18	See **Discontinuation**			**Discontinuation**: - Hair loss and fatigue	*n* 1	% 6
[39]	Cohort [c,l]	**Baseline Age** Adult - Mean NR **CFTR Genotype** NR **Baseline ppFEV$_1$** Mean: 34%	22	**AE in *n* = 3 (14%)**: - Rash - Blurred vision - Viral symptoms	*n* 2 1 1	% 9 5 5	**Discontinued**: - Blurred vision	*n* 1	% 5
Elexacaftor/Tezacaftor/Ivacaftor									
[40]	Retrospective Cohort	**Baseline Age** Adult - Mean: 36 yr **CFTR Genotype** ≥1 copy ΔF508 **Baseline ppFEV$_1$** Mean: 31%	11	- Transaminitis	*n* 4	% 36	None reported		

[a] Rates not reported for all AE, as indicated by 'NS'; [b] To avoid redundancy, if AE only reported in context of dose modification, interruption, and/or discontinuation of therapy, it was not listed in overall AE; [c] Study population part of a compassionate, 'early access', 'expanded access', 'managed access', or 'named patient' program; [d] Total study cohort of *n* = 11, but only *n* = 9 patients completed symptom questionnaire; AE frequency calculated based on total *n* = 11, [e] Mean baseline age and ppFEV$_1$ based on *n* = 135 in final analysis of outcomes assessing effectiveness; *n* = 234 excluded from this analysis; [f] As reported, unable to accurately determine the absolute number of patients who experienced AE; [g] Frequency of specific reasons for interruption or discontinuation not clear and include reasons unrelated to AE; [h] Included age groups (i.e., pediatric and/or adult) not specified; [i] Respiratory failure occurred in 1 individual on two occasions, both within 24 h of initiating and reinitiating LUM/IVA; [j] Of the *n* = 25 who stopped, 9 restarted and 6 of experienced the same AE; unclear which AE the 3 who restarted experienced and whether the 6 who experienced the same AE then discontinued permanently; [k] Mean baseline age and ppFEV$_1$ based on *n* = 23 in final analysis of outcomes assessing effectiveness; *n* = 11 excluded from this analysis; [l] Unable to discern if prospective versus retrospective based on reported information; [m] Total study cohort of *n* = 44, but focused on neurocognitive AE in *n* = 5; AE frequencies calculated based on total *n* = 44. **AST**, aspartate aminotransferase; **CFTR**, cystic fibrosis transmembrane conductance regulator; **CFPEx**, cystic fibrosis pulmonary exacerbation; **GI**, gastrointestinal; **LFT**, liver function test; **LUM/IVA**, lumacaftor/ivacaftor; **NR**, not reported; **NS**, not specified; **ppFEV$_1$,** percent predicted forced expiratory volume in 1 sec; **RA**, rheumatoid arthritis; **SOB**, shortness of breath; **ULN**, upper limit of normal; **URTI**, upper respiratory tract infection; **yr,** year(s).

Table A2. Summary of methodological ratings of included case series [a,b].

Criteria	McKinzie et al., 2017 [47]	Nash et al., 2020 [27]	Rotolo et al., 2020 [52]	Safirstein et al., 2020 [53]	Talwalkar et al., 2017 [48]
1. Study objective clearly stated	Y	Y	N	Y	Y
2. Study population clearly defined, using case definition	N	N	N	N	N
3. Cases consecutive	NR	NR	NR	NR	NR
4. Subjects comparable	CD	CD	CD	N	N
5. Intervention clearly described	Y	Y	Y	Y	Y
6. Outcome measures clearly defined, valid, reliable, implemented consistently	N	N	N	Y	N
7. Adequate length of follow-up	Y	Y	Y	Y	CD
8. Statistical methods well-described	N/A	N/A	N/A	N/A	N
9. Results well-described	Y	N	Y	Y	Y
Final rating	**Poor**	**Poor**	**Fair**	**Good**	**Poor**

[a] Studies were rated against the 9 criteria of the Quality Assessment for Case Series Studies from the National Institutes of Health, National Heart, Lung, and Blood Institute [24] from the standpoint of AE assessment; [b] Only case series with a full manuscript were assessed for quality. **AE**, adverse event; **CD**, cannot determine; **N**, no; **N/A**, not applicable; **NR**, not reported; **Y**, yes.

Reference

1. Dagenais, R.V.E.; Su, V.C.; Quon, B.S. Real-World Safety of CFTR Modulators in the Treatment of Cystic Fibrosis: A Systematic Review. *J. Clin. Med.* **2021**, *10*, 23. [CrossRef]