Common Drug Review
Clinical Review Report

October 2016

Drug	lumacaftor/ivacaftor (Orkambi)
Indication	For the treatment of cystic fibrosis in patients age 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene
Listing request	As per indication
Dosage form(s)	lumacaftor 200 mg/ivacaftor 125 mg tablets
NOC date	January 26, 2016
Manufacturer	Vertex Pharmaceuticals (Canada) Incorporated

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in *cystic fibrosis* who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
BL	baseline
BMI	body mass index
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CF	cystic fibrosis
CF Canada	Cystic Fibrosis Canada
CFQ-R	Cystic Fibrosis Questionnaire–Revised
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
CPK	creatine phosphokinase
DB	double-blind
EMA	European Medicines Agency
EQ-5D-3L	EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire–3 Levels
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FEV_1	forced expiratory volume in one second
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
ITT	intention-to-treat population
IV	intravenous
IVA	ivacaftor
MCID	minimal clinically important difference
MMRM	mixed-effects model for repeated measures
NICE	National Institute for Health and Care Excellence
LABD	long-acting bronchodilator
LOCF	last observation carried forward
LS	least squares
LSMD	least squares mean difference
LUM	lumacaftor

LUM/IVA	lumacaftor/ivacaftor
OR	odds ratio
PLC	placebo
PP	per-protocol
ppFEV$_1$	per cent predicted forced expiratory volume in one second
qd	once daily
q12h	every 12 hours
RCT	randomized controlled trial
SABD	short-acting bronchodilator
SAE	serious adverse event
SD	standard deviation
SE	standard error
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Orkambi is a fixed-dose combination (FDC) tablet containing 200 mg lumacaftor and 125 mg ivacaftor (LUM/IVA). It is indicated for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[1] This is the most common CF-causing mutation worldwide and approximately half of all Canadian patients with CF are homozygous for the F508del mutation.[2,3] LUM/IVA is the first treatment specifically indicated for the treatment of patients who are homozygous for the F508del mutation in the CFTR gene. The manufacturer has requested that LUM/IVA receive a recommendation to list in accordance with the Health Canada–approved indication.

The CADTH Common Drug Review (CDR) conducted a systematic review to evaluate the beneficial and harmful effects of LUM/IVA for the treatment of patients aged 12 years and older with CF and who are homozygous for the F508del mutation in the CFTR gene.

Results and Interpretation

Included Studies

The CDR systematic review included two randomized controlled trials (RCTs). TRAFFIC and TRANSPORT were identically-designed, phase 3, randomized, double-blind, placebo-controlled studies conducted to evaluate the efficacy and safety of LUM/IVA in CF patients who are at least 12 years of age and homozygous for the F508del-CFTR mutation.[4] Both studies included a screening phase (up to 28 days), a double-blind treatment period (24 weeks), and a safety follow-up phase (approximately four weeks). Patients aged 12 years and older were eligible for inclusion in TRANSPORT and TRAFFIC if they were homozygous for the F508del-CFTR mutation and had a confirmed diagnosis of CF, which was defined as sweat chloride value ≥ 60 mmol/L or two CF-causing mutations; and chronic sinopulmonary disease or gastrointestinal and/or nutritional abnormalities. Patients were also required to have stable CF disease and a per cent predicted forced expiratory volume in one second ($ppFEV_1$) of ≥ 40% and ≤ 90% at the time of screening.

Eligible patients were randomized (1:1:1) to one of the following three treatment groups: LUM 600 mg once daily/IVA 250 mg every 12 hours; LUM 400 mg every 12 hours/IVA 250 mg every 12 hours; or placebo. In accordance with the Health Canada–approved dosage regimen for LUM/IVA, the CDR systematic review focused on the results for LUM 400 mg every 12 hours/IVA 250 mg every 12 hours.

The use of placebo as the comparator in TRAFFIC and TRANSPORT is appropriate, as LUM/IVA is a novel treatment for CF patients with F508del-CFTR mutations. Both TRAFFIC and TRANSPORT compared the addition of LUM/IVA or placebo to ongoing standard CF-management therapies, which is reflective of how LUM/IVA would likely be administered in routine clinical practice. The clinical expert consulted by CDR indicated that the background therapies reported in TRAFFIC and TRANSPORT were generally consistent with those used in Canadian clinical practice.

The studies were generally well conducted. The clinical expert noted that the diagnostic criteria that were used in the screening process for TRAFFIC and TRANSPORT were consistent with those used in Canadian clinical practice for the identification of CF patients who are homozygous for the F508del-CFTR mutation. CF patients with more severe lung disease (i.e., $ppFEV_1$ < 40% at screening) or a normal

$ppFEV_1$ at screening (i.e., ≥ 90%) were to be excluded from the studies; therefore, the results of the included studies are primarily applicable to patients with mild to moderate lung disease.

The 24-week treatment periods were sufficient for observing treatment differences in the primary end point and many of the secondary end points in TRAFFIC and TRANSPORT; however, the duration was insufficient to observe whether or not treatment with LUM/IVA has the potential to modify the course of disease for CF patients with F508del-CFTR mutations.

Efficacy

The TRAFFIC and TRANSPORT studies evaluated a range of different outcomes that are considered to be important in the management of CF, including respiratory function, changes in nutritional status and growth, health-related quality of life, and pulmonary exacerbations. After 24 weeks of treatment, LUM/IVA was associated with a statistically significant improvement in $ppFEV_1$ compared with placebo (absolute increase of 2.6% to 3.0%). The treatment effect with LUM/IVA was relatively consistent across all of the subgroups that were studied in TRAFFIC and TRANSPORT; however, there was considerable uncertainty in some analyses due to the small number of patients (e.g., $ppFEV_1$ < 40% or aged 12 to 18 years). In a responder analysis, fewer than one-third of LUM/IVA-treated patients achieved an absolute increase of at least 5% in $ppFEV_1$.

No published information on the minimal clinically important difference (MCID) for the change in $ppFEV_1$ in CF was identified by CDR. The clinical expert consulted for this review indicated that a change in $ppFEV_1$ of the magnitude observed in the TRAFFIC and TRANSPORT studies was of uncertain clinical benefit. While no published information on the MCID in absolute change in $ppFEV_1$ in CF was identified by CDR, the clinical expert consulted by CDR noted that CF specialists would generally consider an absolute improvement in $ppFEV_1$ of ≥ 5% to be clinically significant. International regulatory agencies noted that the magnitude of improvement is "small" to "moderate," but may be clinically relevant for CF patients, given that changes in FEV_1 have been shown to be correlated with mortality.[5-7] In contrast, the committee for the National Institute for Health and Care Excellence (NICE) in the United Kingdom concluded that the improvements in $ppFEV_1$ observed with LUM/IVA in the pivotal studies were unlikely to be clinically significant.[8]

In both TRAFFIC and TRANSPORT, treatment with LUM/IVA was associated with lower rates of the following: pulmonary exacerbations, pulmonary exacerbations requiring hospitalization, and pulmonary exacerbations requiring IV antibiotic therapy. Similarly, hazard ratios for the above-noted end points demonstrated a favourable treatment effect for LUM/IVA compared with placebo. Statistical significance could not be concluded for differences in the number of pulmonary exacerbations, a key secondary end point of pivotal studies, as the statistical testing hierarchy was stopped prior to this outcome. Results for other pulmonary exacerbation assessments were statistically significant, but were analyzed outside of the pre-specified hierarchical analysis plan and may be subject to inflated type 1 error. However, the clinical expert involved in the review indicated that the improvements in pulmonary exacerbations were likely clinically significant. There is consistent reporting from Health Canada, the European Medicines Agency (EMA), the United States Food and Drug Administration (FDA), and NICE that the reduction in pulmonary exacerbations that was observed in the TRAFFIC and TRANSPORT studies is likely to be clinically relevant.[5,6,8]

Given that the treatment with LUM/IVA is systemic, the TRAFFIC and TRANSPORT studies included end points such as body mass index (BMI), body weight, and height to evaluate the effect of treatment on the nutritional status of patients. Results for change from baseline in BMI and weight were inconsistent

across the pivotal studies, with statistically significant improvements observed in TRANSPORT but not in TRAFFIC. Neither study demonstrated a statistically significant difference between LUM/IVA and placebo for changes in the height of CF patients who were younger than 20 years of age.

Treatment with LUM/IVA did not demonstrate statistically significant or clinically relevant improvements in the health-related quality of life end points that were included in the TRAFFIC and TRANSPORT studies (i.e., Cystic Fibrosis Questionnaire–Revised [CFQ-R] and the EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire–3 Levels [EQ-5D-3L]).

Harms

LUM/IVA was generally well tolerated in the TRAFFIC and TRANSPORT study populations. The proportion of patients who experienced at least one serious adverse event (SAE) was greater in the placebo group (28.6%) compared with the LUM/IVA group (17.3%); however, this difference was primarily attributable to the increased occurrence of infective pulmonary exacerbations of CF in the placebo group compared with the LUM/IVA group (24.1% versus 11.1%, respectively). Withdrawals due to adverse events were more common in the LUM/IVA group compared with the placebo group in both pivotal studies (4.6% versus 1.6%, respectively); however, more than 95% of LUM/IVA-treated patients completed the 24-week treatment period.

The overall proportion of patients who experienced at least one adverse event was similar between the placebo groups (95.9%) and the LUM/IVA group (95.1%). The most common adverse events associated with LUM/IVA were respiratory and gastrointestinal. Adverse events that were reported in ≥ 5% of patients in the LUM/IVA group and occurred at higher frequency compared with the placebo group were: dyspnea (13% versus 8%); respiration abnormal (9% versus 6%); rhinorrhea (6% versus 4%); nasopharyngitis (13% versus 11%); upper respiratory tract infection (10% versus 5%); influenza (5% versus 2%); nausea (13% versus 8%); diarrhea (12% versus 8%); flatulence (7% versus 3%); fatigue (9% versus 8%); blood creatine phosphokinase increased (7% versus 5%), and rash (7% versus 2%).

LUM/IVA was associated with an increased incidence of respiratory adverse events (e.g., dyspnea and abnormal respiration) compared with placebo. Nearly all of these events were mild to moderate in severity, occurred shortly after the initiation of treatment, and typically resolved within a few weeks of treatment. The respiratory adverse events occurred more frequently in patients with poorer lung function; however, the severity of these events was generally similar regardless of baseline lung function.[9]

Twenty-four-week data from the PROGRESS extension study (i.e., 48 weeks of LUM/IVA treatment) suggested that patients treated with LUM/IVA maintained the improvements in ppFEV$_1$ that were observed in the double-blind phase of TRAFFIC and TRANSPORT. Patients in the PROGRESS study also continued to demonstrate a lower rate of pulmonary exacerbations compared with the rates observed in the placebo groups of the double-blind studies and showed gradual improvements in BMI and body weight z scores. However, due to the relatively short duration of follow-up, the absence of a control group, and the uncertainty regarding the baseline values used in the interim analysis, conclusions regarding the long-term effectiveness of LUM/IVA cannot be made based on the available data from PROGRESS.

Other Considerations

NICE in the United Kingdom recently issued a draft recommendation (pending final determination in July 2016) stating it does not recommend that LUM/IVA be funded for treating CF in people aged 12 years

and older who are homozygous for the F508del mutation in the CFTR gene.[8] NICE's Technology Appraisal Committee (TAC) noted that the improvements in $ppFEV_1$ observed in the TRAFFIC and TRANSPORT studies were unlikely to be clinically significant, but that the reductions in pulmonary exacerbations were clinically significant. Overall, the TAC concluded that the estimated incremental cost-effectiveness ratios for LUM/IVA exceed the levels that are typically considered to represent a cost-effective use of health care resources. Similarly, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia issued a decision stating that LUM/IVA was not recommended for listing on the Pharmaceutical Benefits Scheme. The committee cited unacceptably high and uncertain incremental cost-effectiveness and uncertainty regarding the impact of LUM/IVA on long-term improvements in lung function and survival for CF patients.[10] The Scottish Medicines Consortium (SMC) also concluded that LUM/IVA was not recommended for use within NHS Scotland. The SMC noted that the cost of LUM/IVA relative to the health benefits it offered was insufficient.[11]

Conclusions

The CDR systematic review included two phase 3 RCTs (TRAFFIC [N=559] and TRANSPORT [N=563]) that investigated the comparative safety and efficacy of LUM/IVA in patients with CF who were 12 years and older with mild to moderate lung disease and who were homozygous for the F508del-CFTR mutation. Both studies demonstrated that 24 weeks of treatment with LUM/IVA was associated with statistically significant improvements in $ppFEV_1$ (absolute increases of 2.6% to 3.0% and relative increases of 4.3% to 4.5%); however, the clinical significance of the improvements is uncertain. An ongoing extension study (PROGRESS) demonstrated that the improvements in $ppFEV_1$ persisted after 48 weeks of treatment. Compared with placebo, LUM/IVA demonstrated clinically meaningful reductions in the number and severity of pulmonary exacerbations, including those that required hospitalization and treatment with IV antibiotics; however, no conclusions about the statistical significance of these outcomes could be made. There was inconsistency in the results for changes in BMI, with statistical significance being demonstrated in only the TRANSPORT trial. A pre-planned pooled analysis; however, suggests that treatment with LUM/IVA was associated with improvements in BMI, although the magnitude of improvement was of uncertain clinical significance. Treatment with LUM/IVA was not associated with statistically significant or clinically relevant improvements in health-related quality of life.

LUM/IVA was generally well tolerated in the study populations, with more than 95% of LUM/IVA-treated patients completing the 24-week treatment period. LUM/IVA was associated with an increased frequency of respiratory adverse events (e.g., dyspnea and abnormal respiration) compared with placebo; however, these events were typically mild to moderate in severity and occurred shortly after the initiation of treatment.

TABLE 1: SUMMARY OF KEY EFFICACY RESULTS

	TRAFFIC		TRANSPORT		Pooled	
	Placebo	LUM/IVA	Placebo	LUM/IVA	Placebo	LUM/IVA
Absolute change in $ppFEV_1$ (%) at 16 and 24 weeks						
BL; mean (SD)	60.45 (13.221)	60.48 (14.289)	60.37 (14.318)	60.59 (14.014)	60.41 (13.767)	60.54 (14.131)
LSM change (SE)	−0.44 (0.524)	2.16 (0.530)	−0.15 (0.539)	2.85 (0.540)	−0.32 (0.376)	2.49 (0.379)
LSMD (95% CI)[a]	2.6 (1.8 to 4.0)		3.0 (1.6 to 4.4)		2.81 (1.80 to 3.82)	
P value	0.0003		< 0.0001		< 0.0001	
≥ 5% increase in absolute change in $ppFEV_1$ (%) at 16 and 24 weeks						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)[c]	[redacted]		[redacted]		[redacted]	
P value	[redacted]		[redacted]		[redacted]	
Relative change in $ppFEV_1$ (%) at 16 and 24 weeks						
BL; mean (SD)	60.45 (13.221)	60.48 (14.289)	60.37 (14.318)	60.59 (14.014)	60.41 (13.767)	60.54 (14.131)
LSM change (SE)	−0.34 (0.913)	3.99 (0.923)	0.00 (0.960)	5.25 (0.961)	−0.17 (0.662)	4.64 (0.666)
LSMD (95% CI)[a]	4.33 (1.86 to 6.80)		5.25 (2.69 to 7.81)		4.81 (3.03 to 6.59)	
P value	0.0006		< 0.0001		< 0.0001	
≥5% increase in relative change in $ppFEV_1$ (%) at 16 and 24 weeks						
n (%)	41 (22.3)	67 (36.8)	42 (22.5)	77 (41.2)	83 (22.4)	144 (39.0)
OR (95% CI)[c]	2.06 (1.29 to 3.28)		2.38 (1.52 to 3.73)		2.22 (1.61 to 3.07)	
P value	0.0023[b]		0.0001[b]		< 0.0001	
Any pulmonary exacerbation through 24 weeks						
Events (per year)	112 (1.07)	73 (0.71)	139 (1.18)	79 (0.67)	251 (1.14)	152 (0.70)
Rate ratio (95% CI)[d]	0.66 (0.47 to 0.93)		0.57 (0.42 to 0.76)		0.61 (0.49 to 0.76)	
P value	0.0169[b]		0.0002[b]		< 0.0001	
Pulmonary exacerbations requiring hospitalization through 24 weeks						
Events (per year)	46 (0.36)	17 (0.14)	59 (0.46)	23 (0.18)	105 (0.45)	40 (0.17)
Rate ratio (95% CI)[d]	0.38 (0.22 to 0.67)		0.39 (0.24 to 0.64)		0.39 (0.26 to 0.56)	

	TRAFFIC		TRANSPORT		Pooled	
	Placebo	LUM/IVA	Placebo	LUM/IVA	Placebo	LUM/IVA
P value	0.0008		0.0002		< 0.0001	
Pulmonary exacerbations requiring IV antibiotics through 24 weeks						
Events (per year)	62 (NA)	33 (NA)	87 (0.64)	31 (0.23)	149 (0.58)	64 (0.25)
Rate ratio (95% CI)[d]	No estimate		0.36 (0.24 to 0.54)		0.44 (0.32 to 0.59)	
P value	0.0050		< 0.0001		< 0.0001	
Time to first pulmonary exacerbation through 24 weeks						
n (%)	73 (39.7)	55 (30.2)	88 (47.1)	54 (28.9)	161 (43.4)	109 (29.5)
Hazard ratio [e]	0.691 (95% CI, NR)		0.533		0.607 (95% CI, NR)	
P value	0.0385		0.0003		< 0.0001	
BMI (kg/m^2) at 24 weeks						
BL; mean (SD)	21.03 (2.956)	21.68 (3.169)	21.02 (2.887)	21.32 (2.894)	21.02 (2.918)	21.50 (3.034)
LSM change (SE)	0.19 (0.070)	0.32 (0.071)	0.07 (0.066)	0.43 (0.066)	0.13 (0.048)	0.37 (0.048)
LSMD (95% CI)	0.13 (−0.07 to 0.32)		0.36 (0.17 to 0.54)		0.24 (0.11 to 0.37)	
P value	0.1938		0.0001		0.0004	
BMI z score at 24 weeks						
BL; mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (SE)	0.015 (0.049)	0.093 (0.054)	−0.067 (0.047)	0.154 (0.045)	[redacted]	[redacted]
LSMD (95% CI)[a]	0.078 (−0.062 to 0.218)		0.222 (0.096 to 0.347)		[redacted]	
P value	0.2713		0.0006		[redacted]	
Weight (kg) at 24 weeks						
BL; mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (SE)	0.93 (0.202)	1.23 (0.205)	0.44 (0.187)	1.38 (0.187)	0.69 (0.138)	1.31 (0.139)
LSMD (95% CI)[a]	0.30 (−0.26 to 0.86)		0.95 (0.43 to 1.46)		0.62 [redacted]	
P value	0.2992		0.0003		0.0013	

	TRAFFIC		TRANSPORT		Pooled	
	Placebo	LUM/IVA	Placebo	Placebo	LUM/IVA	Placebo
CFQ-R (Respiratory Domain) at 24 weeks						
BL; mean (SD)	70.54 (16.032)	69.29 (17.424)	67.05 (18.394)	67.36 (18.540)	68.78 (17.328)	68.31 (17.998)
LSM change (SE)	1.10 (1.161)	2.60 (1.192)	2.81 (1.153)	5.66 (1.169)	1.88 (0.818)	4.10 (0.834)
LSMD (95% CI)[a]	1.50 (−1.69 to 4.69)		2.85 (−0.27 to 5.98)		2.22 (−0.01 to 4.45)	
P value	0.3569[a]		0.0736		0.0512	
EQ-5D-3L (utility score) at 24 weeks						
BL; mean (SD)	0.9237 (0.10371)	0.9217 (0.09774)	0.9171 (0.10837)	0.9267 (0.10462)	Not pooled	
LSM change (SE)	0.0006 (0.0074)	0.01 (0.0076)	0.0117 (0.00673)	0.0108 (0.00683)		
LSMD (95% CI)[a]	0.0095 (−0.0109 to 0.0298)		−0.0009 (−0.0192 to 0.0174)			
P value	0.3613		0.9214			
EQ-5D-3L (VAS) at 24 weeks						
BL; mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	Not pooled	
LSM change (SE)	1.4 (1.03)	2.8 (1.04)	3.3 (1.07)	6.6 (1.08)		
LSMD (95% CI)[a]	1.4 (−1.3 to 4.2)		3.3 (0.4 to 6.2)			
P value	0.3071		0.0262			

BL = baseline; BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire–Revised; CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire–3 Levels; IV = intravenous; LSM = least squares mean; LSMD = least squares mean difference; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients with events; NR = not reported; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; q12h = every 12 hours; SD = standard deviation; SE = standard error; VAS = visual analogue scale.

[a] Mixed-effects model for repeated measures that included covariate adjustment for sex, age group at baseline (< 18 versus ≥ 18 years), and $ppFEV_1$ at screening (< 70% versus ≥ 70%). Continuous end points other than $ppFEV_1$ were also adjusted for the baseline value of the dependent variable (e.g., baseline BMI).[12,13]

[b] These were pre-specified key secondary end points; therefore, the statistical testing hierarchy was enforced for this end point and no conclusions with respect to statistical significance for this end point can be made.

[c] Stratified by sex, age group at baseline (< 18 versus ≥ 18 years), and $ppFEV_1$ at screening (< 70% versus ≥ 70%).[12,13]

[d] Treatment comparison was conducted using regression analysis for a negative binomial distribution with sex, age group at baseline (< 18 versus ≥ 18 years), and $ppFEV_1$ at screening (< 70% versus ≥ 70%) as covariates with the logarithm of time on study as the offset.[12,13]

[e] Adjustment for sex, age group at baseline (< 18 versus ≥ 18 years), and $ppFEV_1$ at screening (< 70% versus ≥ 70%).

Sources: Wainwright et al., 2015,[14] Common Technical Document sections 2.7.4[15] and 5.3.5.3,[16] and Clinical Study Reports for TRAFFIC[12] and TRANSPORT.[13]

TABLE 2: SUMMARY OF ADVERSE EVENTS

AEs, n (%)	TRAFFIC		TRANSPORT		Pooled	
	Placebo	LUM/IVA	Placebo	LUM/IVA	Placebo	LUM/IVA
Any AEs	174 (94.6)	174 (95.6)	181 (97.3)	177 (94.7)	355 (95.9)	351 (95.1)
SAEs	49 (26.6)	33 (18.1)	57 (30.6)	31 (16.6)	106 (28.6)	64 (17.3)
WDAEs	4 (2.2)	6 (3.3)	2 (1.1)	11 (5.9)	6 (1.6)	17 (4.6)
AEs leading to interruption	[redacted]	[redacted]	[redacted]	[redacted]	25 (6.8)	22 (6.0)
Grade 3 or 4 AEs	[redacted]	[redacted]	[redacted]	[redacted]	59 (15.9)	45 (12.2)
AESI of respiratory symptoms	[redacted]	[redacted]	[redacted]	[redacted]	51 (13.8)	81 (22.0)
AEs leading to death	0	0	0	0	0	0

AE = adverse event; AESI = adverse event of special interest; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients with events; q12h = every 12 hours; SAE = serious adverse event; WDAE = withdrawal due to adverse events

Sources: Wainwright et al., 2015,[14] Common Technical Document sections 2.7.4,[15] and Clinical Study Reports for TRAFFIC[12] and TRANSPORT.[13]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Cystic fibrosis (CF), an autosomal recessive condition, is the most common fatal genetic disease affecting children and young adults in Canada.[17,18] It is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, located on chromosome 7. The CFTR gene encodes a chloride channel that regulates ion and fluid transport across cell membranes.[17,18] When CFTR is dysfunctional, secretions become tenacious and sticky, resulting in pathology in multiple organs, including the lungs, large and small intestine, pancreatic and bile ducts, and the vas deferens.[17] A deletion of phenylalanine 508 in NBD1 (F508del) is the most common mutation that results in CF.[2,3] According to the Canadian Cystic Fibrosis Registry, 50.0% of the 3,972 CF patients in the registry were homozygous for F508del mutations and 89.7% of patients had at least one F508del mutation.[3]

More than 1,900 CFTR variants have been identified among CF patients.[17,18] The CFTR variants have been classified as impaired biosynthesis (class I); defective protein maturation and accelerated degradation (class II); defective regulation of CFTR at the plasma membrane (class III); defective chloride conductance (class IV); diminished CFTR transcription (class V); and accelerated turnover at the cell surface (class VI).[17] CFTR variants within classes I to III are associated with severe CF, as they are considered non-functional, while CFTR variants in classes IV to VI may retain CFTR function.[17] The F508del mutation is typically considered a class II CFTR mutation and is a severe mutation resulting in significant loss of function of the CFTR protein. The F508del defect causes CFTR to misfold resulting in the majority of the protein being removed before it can reach the cell membrane. In addition, the F508del-CFTR confers defects in gating as well as being unstable and having more rapid turnover at the cell membrane.[19,20] Genotyping for mutations in the CFTR gene is routinely performed on almost all CF patients in Canada and is part of the newborn screening process.

CF results in airway obstruction, chronic endobronchial infection, and inflammation, which ultimately leads to destruction of lung tissue with development of bronchiectasis and loss of lung function.[21] Lung disease accounts for 85% of mortality[21] and in 2013, the median age of survival for Canadians with CF was estimated to be 50.9 years of age[3] Chronic endobronchial infection of the airways with bacterial pathogens, such as *Pseudomonas aeruginosa*, which occurs in almost half of individuals with CF,[3] is associated with a more rapid loss of lung function.[22] Acute or chronic endobronchial infections result in further destruction of lung tissue and are associated with respiratory morbidity. Maintenance of pulmonary function (higher FEV_1) and fewer respiratory exacerbations are associated with increased survival.[23] Pulmonary management of CF therefore aims to clear the airways of secretions and treat lung pathogens to minimize inflammation.

Gastrointestinal and pancreatic involvement results in pancreatic exocrine insufficiency in the majority of individuals with CF, causing malabsorption of fats and fat-soluble vitamins, which leads to malnutrition. Maintaining adequate nutrition is associated with improved clinical outcome and longevity for CF patients.[24]

Patients who are homozygous for F508del mutation typically have pancreatic, gastrointestinal, and nutritional disease, as well as progressive pulmonary damage. Virtually all will be pancreatic insufficient and need to take lifelong pancreatic enzyme replacement with every meal, as well as fat-soluble vitamin therapy. With increasing age, these patients will develop CF-related diabetes and require therapy with

insulin. Approximately 30% and 40% of patients aged 30 years and 40 years, respectively, will have diabetes.[3]

Although chronic pulmonary therapies, instituted early in the disease, have reduced the decline in lung function over time, patients who are homozygous for the F508del mutation will develop chronic infection with *Pseudomonas aeruginosa,* progressive bronchiectasis, and airway obstruction. Pulmonary exacerbations are associated with mortality and lung function decline and a third of patients will have at least one pulmonary exacerbation per year requiring intravenous (IV) antibiotics.[25] In a cohort of approximately 1,000 healthy young children with CF who did not have *Pseudomonas* infection at enrolment, there was a greater annual decline in FEV_1 over the following four years in those who were homozygous for the F508del mutation.[26] The median age of death for CF patients in Canada is 35.1 years.[3] There is a clear unmet need for better CF therapies.

1.2 Standards of Therapy

The goals of CF therapy include the following: (1) preservation of lung function by minimizing pulmonary infection and inflammation; (2) restoration of baseline pulmonary function, symptoms, and level of inflammation after acute respiratory exacerbations; and (3) maintenance of adequate nutrition. Respiratory treatments consist of physiotherapy and pharmacologic drugs that are antibiotics, anti-inflammatory drugs, or mucolytics.[27] Nutritional treatments consist of high-calorie and high-fat diets,[28] and for those with pancreatic insufficiency, pancreatic enzyme replacement.

The choice of a therapeutic regimen for CF depends on organ involvement. The severity of lung function impairment and the presence of bacterial pathogens are deterministic factors when selecting chronic pulmonary therapy. Patients who are homozygous for F508del are advised to perform chest physiotherapy and exercise, and use mucolytics (e.g., hypertonic saline and/or dornase alfa). If they are chronically infected with *Pseudomonas*, standard of care is to use inhaled antibiotics and macrolide anti-inflammatory agents.[27] Pulmonary exacerbations are treated with oral or IV antibiotics. These treatments do not halt, but only slow, the decline in lung function and the progression of disease.

1.3 Drug

1.3.1 Indication and Requested Listing Criteria

LUM/IVA is indicated for the treatment of CF in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.[1] The manufacturer has requested that LUM/IVA receive a recommendation to list in accordance with the Health Canada–approved indication (Table 3).

TABLE 3: INDICATION AND REQUESTED LISTING CRITERIA

Indication under review
For the treatment of cystic fibrosis in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene.
Listing criteria requested by the applicant
As per indication

CFTR = cystic fibrosis transmembrane conductance regulator.

1.3.2 Recommended Dosage

The product monograph recommends a dose of two tablets (each containing LUM 200 mg/IVA 125 mg) taken orally every 12 hours with fat-containing food. The monograph indicates that dosage adjustment is not required for patients with mild hepatic impairment, but is recommended for patients with moderate and severe hepatic impairment (Table 4).[1]

When used in combination with LUM in patients who are homozygous for the F508del mutation, the daily dosage of IVA is greater (i.e., 500 mg per day) compared with the dosage of IVA monotherapy used in patients with CFTR gating mutations (i.e., 300 mg per day). This is due to the induction of cytochrome P4503A caused by LUM, which results in a reduction in overall IVA exposure.[5]

TABLE 4: RECOMMENDED DOSAGE ADJUSTMENT FOR HEPATIC IMPAIRMENT

Hepatic Insufficiency	Dose Adjustment	Total Daily Dose
Mild (Child-Pugh Class A)	No dose adjustment	800 mg LUM + 500 mg IVA
Moderate (Child-Pugh Class B)	2 tablets (morning) + 1 tablet (evening)	600 mg LUM + 375 mg IVA
Severe (Child-Pugh Class C)	1 tablet (morning) + 1 tablet (evening)	400 mg LUM + 250 mg IVA

IVA = ivacaftor; LUM = lumacaftor.
Source: Adapted from the Orkambi product monograph.[1]

1.3.3 Mechanism of Action

LUM/IVA is the first treatment specifically indicated for the treatment of patients who are homozygous for the F508del mutation in the CFTR gene. This particular mutation is believed to be associated with misfolding of the of CFTR protein, which results to a lower quantity of CFTR expression at the cell surface. In addition to the reduced quantity of the protein, the mutation results in CFTR that is less stable and has defective channel gating compared to wild-type CFTR.

The mechanism of action for LUM/IVA is reported as follows:[1]

- Lumacaftor improves the conformational stability of F508del-CFTR protein, resulting in an increased expression of the F508del-CFTR protein at the cell surface.
- Ivacaftor increases the channel-open probability of the CFTR protein at the cell surface.

1.4 Previous Reviews by the CADTH Common Drug Review

Ivacaftor has been reviewed through the CADTH Common Drug Review (CDR) process for the following indications:

- Patients aged six years or older who have a G551D mutation in the CFTR gene[17]
- Patients aged six years or older who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R[29]
- Patients aged 18 years or older who have a R117H mutation in the CFTR gene.[18]

For each of the above-noted indications, the CADTH Canadian Drug Expert Committee (CDEC) recommended that ivacaftor be listed with clinical criteria and/or conditions.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of LUM 400 mg/IVA 250 mg every 12 hours for the treatment of patients aged 12 years and older who have CF and who are homozygous for the F508del mutation in the CFTR gene.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 5.

TABLE 5: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients aged 12 years and older who have CF and who are homozygous for the F508del mutation in the CFTR gene Subgroups: • Severity of disease (based on baseline FEV_1) • Age
Intervention	• LUM 400 mg every 12 hours + IVA 250 mg every 12 hours (orally)
Comparators	• Standard of care (may include antibiotics, anti-inflammatory drugs, mucolytic drugs, pancreatic enzymes, and physiotherapy) • Placebo
Outcomes	**Key efficacy outcomes:** • Mortality/survival • Disease progression (based on FEV_1)[a] • Acute pulmonary exacerbations or infection[a] • Health-related quality of life[a] • Functional capacity[a] **Other efficacy outcomes:** • Hospitalization[a] • Weight[a] • Body mass index • Changes in concomitant CF medications[a] • Sweat chloride levels **Harms outcomes:** • Adverse events, serious adverse events, withdrawal due to adverse events • Notable harms: hepatic adverse events, respiratory adverse events
Study Design	Published and unpublished randomized controlled trials (excluding phase 2 and below studies, if not considered pivotal)

CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; FEV_1 = forced expiratory volume in 1 second; IVA = ivacaftor; LUM = lumacaftor.
[a]These outcomes were identified as being important to patients based on the patient input received.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH

(Medical Subject Headings), and keywords. The main search concepts were Orkambi (lumacaftor/ivacaftor).

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See APPENDIX 2: LITERATURE SEARCH STRATEGY for the detailed search strategies.

The initial search was completed on February 25, 2016. Regular alerts were established to update the search until the CDEC meeting (targeting June 15, 2016). Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases (free), and Internet search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 6; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of two studies (TRAFFIC and TRANSPORT) were identified from the literature for inclusion in the systematic review (Figure 1). In addition to these two studies, the CDR review also provides a summary of a pooled analysis of the TRAFFIC and TRANSPORT studies and the PROGRESS longer-term extension study. The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

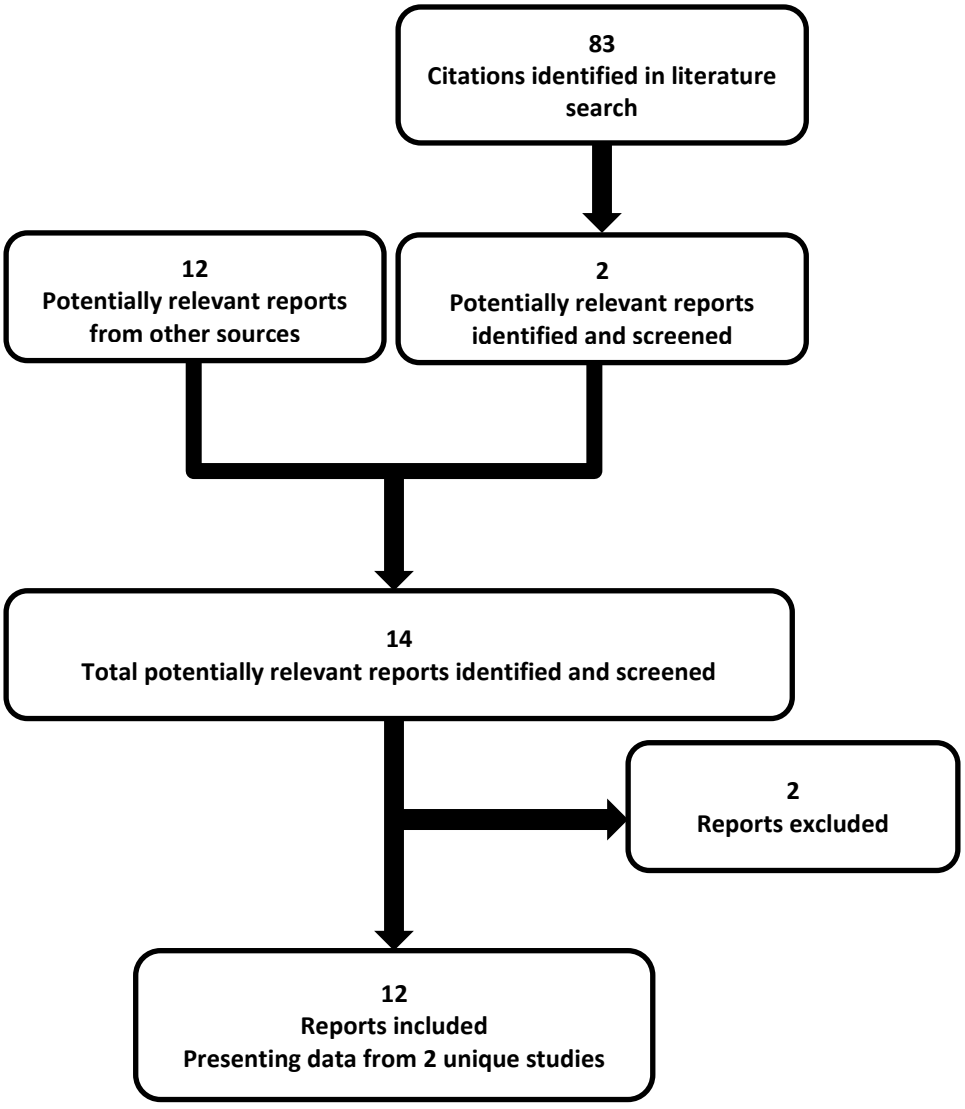


TABLE 6: DETAILS OF INCLUDED STUDIES

		TRAFFIC	TRANSPORT
DESIGNS & POPULATIONS	**Study Design**	Phase 3, placebo-controlled, DB RCT	Phase 3, placebo-controlled, DB RCT
	Locations	North America, Europe, and Australia (96 sites)	North America, Europe, and Australia (91 sites)
	Randomized (N)	559 (1:1:1)	563 (1:1:1)

	Inclusion Criteria	• Males and females, aged 12 years or older
		• Confirmed diagnosis of CF defined as:
		  ○ sweat chloride value ≥ 60 mmol/L *or* 2 CF-causing mutations *and*
		  ○ chronic sinopulmonary disease *or* gastrointestinal/nutritional abnormalities.
		• Homozygous for the F508del-CFTR mutation
		• FEV_1 ≥ 40% and ≤ 90% of predicted normal for age, sex, and height
		• Stable CF disease
		• Willing to remain on a stable CF medication.	

	Exclusion Criteria	• An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before first dose of study drug
		• History of solid organ or hematological transplantation
		• Use of strong inhibitors, moderate inducers, or strong inducers of CYP450 3A within 14 days
		• Colonization with *Burkholderia cenocepacia*, *B. dolosa*, or *Mycobacterium abscessus*
		• Any of the following abnormal laboratory values:
		  ○ Hemoglobin < 10 g/dL
		  ○ Abnormal liver function, defined as any 3 or more of the following: ≥ 3 × ULN AST, ≥ 3 × ULN ALT, ≥ 3 × ULN GGT, ≥ 3 × ULN ALP, or ≥ 2 × ULN total bilirubin
		  ○ Abnormal renal function, defined as GFR ≤ 50 mL/min/1.73 m^2 for patients aged ≥ 18 years and ≤ 45 mL/min/1.73 m^2 for patients aged 12 to 17 years.	

DRUGS	**Intervention**	• LUM 600 mg qd + IVA 250 mg q12h[a] • LUM 400 mg q12h + IVA 250 mg q12h	
	Comparator(s)	Matching placebo	
	Phase		
	Screening	28 days	28 days
	Double-blind	24 weeks	24 weeks
	Follow-up	4 weeks	4 weeks
OUTCOMES	**Primary End Point**	Absolute change from baseline in $ppFEV_1$ at 24 weeks	

	Other End Points	• Relative change from baseline in $ppFEV_1$
		• Absolute change from baseline in BMI
		• Absolute change from baseline in CFQ-R
		• Percentage with ≥ 5% increase from baseline in $ppFEV_1$
		• Pulmonary exacerbations
		  ○ Number of events
		  ○ Time to first pulmonary exacerbation
		  ○ Participants with ≥ 1 pulmonary exacerbation event
		• Absolute change from baseline in weight
		• Absolute change from baseline in BMI-for-age z score
		• Absolute change from baseline in EQ-5D-3L Index and VAS scores
		• Absolute change from baseline in TSQM domain scores
		• Adverse events, serious adverse events, withdrawals due to adverse events	

NOTES	**Publications**	Wainwright et al., 2015[30] Clinical Study Report[12] Common Technical Document[15,31] Clinicaltrials.gov (NCT01807923)[32]	Wainwright et al., 2015[30] Clinical Study Report[13] Common Technical Document[15,31] Clinicaltrials.gov (NCT01807949)[33]

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; CF = cystic fibrosis; CDR = CADTH Common Drug Review; CFQ-R = Cystic Fibrosis Questionnaire–Revised; DB = double-blind; EQ-5D-3L = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire–3 Levels; GFR = glomerular filtration rate; GGT = gamma-glutamyl transferase; IVA = ivacaftor; LUM = lumacaftor; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; qd = once daily; q12h = every 12 hours; RCT = randomized controlled trial; TSQM = Treatment Satisfaction Questionnaire for Medication; ULN = upper limit of normal; VAS = visual analogue scale.

[a] In accordance with the Health Canada–approved dosage regimen for LUM/IVA, the CDR systematic review focused on the results for LUM 400 mg q12h/IVA 250 mg q12h; therefore, data for the LUM 600 mg qd/IVA 250 mg q12h dosage regimen are not summarized.

3.2 Included Studies

3.2.1 Description of Studies

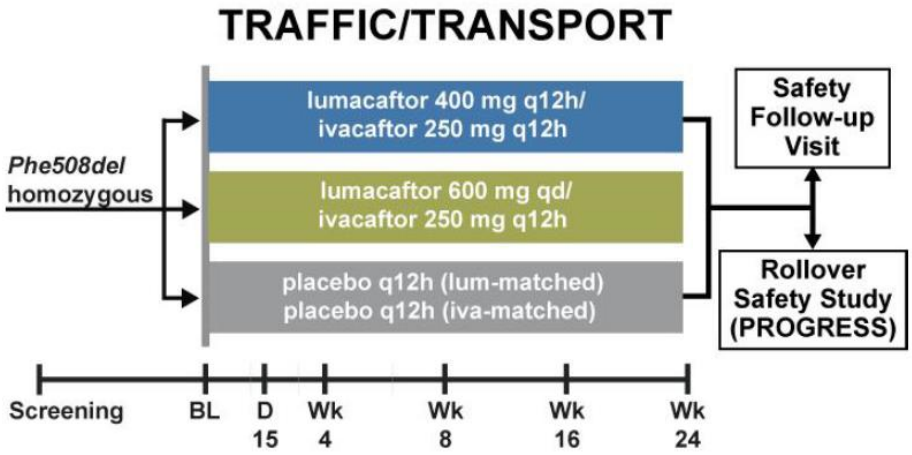
TRAFFIC and TRANSPORT were identically-designed phase 3, randomized, double-blind, placebo-controlled studies conducted to evaluate the efficacy and safety of LUM/IVA in patients with CF who were at least 12 years of age and who were homozygous for the F508del-CFTR mutation. As shown in Figure 2, both studies included a screening phase (up to 28 days), a double-blind treatment period (24 weeks), and a safety follow-up phase (approximately 4 weeks).[31] The manufacturer reported that the only differences in the design of TRAFFIC and TRANSPORT were the following: an ambulatory electrocardiogram was performed only in a subgroup of patients in TRAFFIC; and an intensive pharmacokinetic sampling was performed only in a subgroup of patients in TRANSPORT.[15]

Eligible patients were randomized (1:1:1) to one of the following three treatment groups:

- LUM 600 mg once daily/IVA 250 mg every 12 hours
- LUM 400 mg every 12 hours/IVA 250 mg every 12 hours (LUM/IVA)
- Placebo.

In accordance with the Health Canada–approved dosage regimen for LUM/IVA in patients aged 12 years and older , the CDR systematic review focused on the results for LUM 400 mg every 12 hours/IVA 250 mg every 12 hours (lumacaftor 800 mg/ivacaftor 500 mg total daily dose); therefore, data for the LUM 600 mg once daily/IVA 250 mg every 12 hours dosage regimen are not summarized.

FIGURE 2: SCHEMATIC SHOWING DESIGN OF TRAFFIC AND TRANSPORT



Iva = ivacaftor; lum = lumacaftor; qd = once daily; q12h = every 12 hours.
Source: "From The New England Journal of Medicine, Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al., Lumacaftor-Ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR, 373, 220-241. Copyright ©2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society."

3.2.2 Populations

a) Inclusion and exclusion criteria

Patients aged 12 years and older were eligible for inclusion in TRANSPORT and TRAFFIC if they were homozygous for the F508del-CFTR mutation and had a confirmed diagnosis of CF, which was defined as sweat chloride value ≥ 60 mmol/L *or* two CF-causing mutations; *and* chronic sinopulmonary disease *or* gastrointestinal *and/or* nutritional abnormalities. Patients were also required to have stable CF disease and a $ppFEV_1$ of ≥ 40% and ≤ 90% at the time of screening.[31]

The trials excluded patients with a history of colonization with *Burkholderia cenocepacia*, *B. dolosa*, and/or *Mycobacterium abscessus*. Patients were also considered to be ineligible if they reported an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within four weeks before first dose of study drug. Patients with a history of solid organ or hematological transplantation were excluded, as were patients with abnormal laboratory values (e.g., hemoglobin < 10 g/dL), abnormal liver function, or abnormal renal function.[31]

Randomization was stratified by age (< 18 versus ≥ 18 years of age), sex (male versus female), and disease severity as assessed by $ppFEV_1$ (< 70% versus ≥ 70%) at screening.[31]

b) Baseline characteristics

Table 7 summarizes key baseline and demographic characteristics for the study populations of TRAFFIC and TRANSPORT. The patient characteristics were generally similar across the two studies and across the treatment groups within the studies. A majority of participants were recruited from North America (52.6% and 62.4% in TRAFFIC and TRANSPORT, respectively). There were 29 patients in TRAFFIC and 14 patients in TRANSPORT who were enrolled at Canadian sites. Nearly all participants in both studies were white (98.2% and 99.1% in TRAFFIC and TRANSPORT, respectively). The median age of participants was 23 years in TRAFFIC and 24 years in TRANSPORT. The proportion of patients who were between the ages of 12 and 18 years was greater in TRAFFIC (28.8%) than in TRANSPORT (23.6%). There was a slightly greater proportion of males in TRAFFIC than in TRANSPORT (53.7% versus 47.9%; the pooled average was 50.8%).[31]

TABLE 7: SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics	TRAFFIC		TRANSPORT	
	Placebo (N = 184)	LUM/IVA (N = 182)	Placebo (N = 187)	LUM/IVA (N = 187)
Sex, n (%)				
male	100 (54.3)	98 (53.8)	90 (48.1)	89 (47.6)
female	84 (45.7)	84 (46.2)	97 (51.9)	98 (52.4)
Age, years				
mean (SD)	25.0 (10.8)	25.5 (10.09)	25.7 (10.02)	25.0 (9.03)
median (range)	22.0 (12, 64)	23.5 (12, 57)	24.0 (12, 55)	24.0 (12, 54)
Age category, years, n (%)				
12 to < 18	53 (28.8)	52 (28.6)	43 (23.0)	46 (24.6)
≥ 18	131 (71.2)	130 (71.4)	144 (77.0)	141 (75.4)
Race, n (%)				
White	183 (99.5)	176 (96.7)	186 (99.5)	185 (98.9)
Black	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Region, n (%)				
North America	99 (53.8)	91 (50.0)	122 (65.2)	111 (59.4)
Europe	72 (39.1)	75 (41.2)	49 (26.2)	59 (31.6)
Australia	13 (7.1)	16 (8.8)	16 (8.6)	17 (9.1)
Weight , kg, mean (SD)	59.09 (11.7)	60.62 (12.2)	58.46 (13.1)	59.19 (12.1)
BMI, kg/m^2, mean (SD)[a]	21.03 (3.0)	21.68 (3.2)	21.02 (2.9)	21.32 (2.9)
ppFEV$_1$, %				
mean (SD)	60.45 (13.2)	60.48 (14.3)	60.37 (14.3)	60.59 (14.0)
min, max	34.0, 88.0	34.8, 94.0	33.9, 99.8	31.3, 96.5
< 40	11 (6.0)	12 (6.6)	17 (9.1)	17 (9.1)
≥ 40 to < 70	122 (66.3)	116 (63.7)	116 (62.0)	117 (62.6)
≥ 70 to ≤ 90	48 (26.1)	51 (28.0)	49 (26.2)	49 (26.2)
> 90	0 (0.0)	1 (0.5)	3 (1.6)	2 (1.1)
FEV$_1$, L				
mean (SD)	2.167 (0.62)	2.159 (0.64)	2.136 (0.72)	2.135 (0.62)
median (range)	2.110 (0.87, 3.74)	2.095 (0.96, 3.92)	2.060 (0.79, 4.68)	2.080 (0.96, 3.77)
Pseudomonas aeruginosa, n (%)	134 (72.8)	151 (83.0)	142 (75.9)	135 (72.2)

BMI = body mass index; FEV$_1$ = forced expiratory volume in 1 second; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients; ppFEV$_1$ = per cent predicted forced expiratory volume in one second; q12h = every 12 hours; SD = standard deviation.

[a] BMI was calculated for all patients using the formula: weight (kg)/(height [m])^2

Source: Clinical Study Reports for TRAFFIC[12] and TRANSPORT.[13]

Baseline values were nearly identical in TRAFFIC and TRANSPORT (respectively) for $ppFEV_1$ (60.70% and 60.49%) and BMI (21.25 kg/m^2 and 21.10 kg/m^2). The majority of study participants in TRAFFIC and TRANSPORT had a baseline $ppFEV_1$ between 40% and 70% (65.6% and 63.0%, respectively). Baseline $ppFEV_1$ values between 70% and 90% were reported for 26.6% and 26.7% of patients in TRAFFIC and TRANSPORT, respectively. A small minority of patients in TRAFFIC and TRANSPORT (respectively) had a baseline $ppFEV_1$ below 40% (6.4% and 8.2%) or above 90% (0.4% and 1.3%).[31]

The patient characteristics were similar between the placebo and LUM/IVA groups of both studies. A larger proportion of patients were positive for *P. aeruginosa* in the LUM/IVA group (83.0%) compared with the placebo group (72.8%) in TRAFFIC.

Table 8 summarizes the prior CF medications used in the study populations. The usage of some concomitant medications was more common in TRANSPORT than in TRAFFIC, including dornase alfa (80.1% versus 72.3%), pancreatin (75.3% versus 66.1%), and azithromycin (67.4% versus 58.7%). Concomitant use of salbutamol (69.9% versus 71.6%) and sodium chloride (68.3% versus 66.8%) was similar in TRANSPORT and TRAFFIC, respectively. In TRAFFIC, a greater proportion of patients in the placebo group received dornase alfa before the first dose of study drug (73.4%) compared with LUM/IVA (67.6%). The proportion of study participants who were receiving inhaled antibiotics at baseline was greater in the placebo groups (66.3% to 72.7%) compared with the LUM/IVA groups (59.9% to 62.1%) in both TRAFFIC and TRANSPORT.[31]

TABLE 8: PRIOR USE OF MEDICATIONS FOR CYSTIC FIBROSIS

Prior Medication, n (%)	TRAFFIC		TRANSPORT	
	Placebo (N = 184)	LUM/IVA (N = 182)	Placebo (N = 187)	LUM/IVA (N = 187)
Dornase alfa	135 (73.4)	123 (67.6)	146 (78.1)	150 (80.2)
Inhaled antibiotic	122 (66.3)	113 (62.1)	136 (72.7)	112 (59.9)
Azithromycin	112 (60.9)	97 (53.3)	130 (69.5)	119 (63.6)
Bronchodilator	172 (93.5)	173 (95.1)	170 (90.9)	171 (91.4)
Inhaled bronchodilator	172 (93.5)	171 (94.0)	170 (90.9)	169 (90.4)
SABD only	76 (41.3)	81 (44.5)	78 (41.7)	73 (39.0)
SABD and LABD or LABD only	96 (52.2)	90 (49.5)	92 (49.2)	96 (51.3)
Inhaled hypertonic saline	100 (54.3)	112 (61.5)	120 (64.2)	115 (61.5)
Inhaled corticosteroids	113 (61.4)	109 (59.9)	107 (57.2)	103 (55.1)

LABD = long-acting bronchodilator; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients; q12h = every 12 hours; SABD = short-acting bronchodilator.
Source: Reproduced from Common Technical Document section 2.7.3.[31]

3.2.3 Interventions

The following tablets were used to administer the required dosages in the TRAFFIC and TRANSPORT studies:

- LUM 200 mg/IVA 83 mg (and matching placebo)
- LUM 200 mg/IVA 125 mg (and matching placebo)
- IVA 125 mg (and matching placebo).

In order to maintain blinding, study participants in the active treatment groups were required to receive placebo tablets to ensure that all participants took the same number and type of tablets each day (i.e.,

five tablets in the morning and four tablets in the evening). The daily dosage schedule for TRAFFIC and TRANSPORT is summarized in Table 9. All study drugs were to be administered within 30 minutes of consuming fat-containing food. The study drugs were to be provided in addition to the participant's currently prescribed CF therapy.[31]

TABLE 9: SUMMARY OF STUDY DRUG ADMINISTRATION IN TRANSPORT AND TRAFFIC

Treatment Group	Time	Tablets Administered					
		LUM/IVA (200 mg/125 mg)		LUM/IVA (200 mg/83 mg)		IVA (125 mg)	
		Active	Placebo	Active	Placebo	Active	Placebo
LUM 600 mg qd/ IVA 250 mg q12h	a.m.	—	2	3	—	—	—
	p.m.	—	2	—	—	2	—
LUM 400 mg q12h/ IVA 250 mg q12h	a.m.	2	—	—	3	—	—
	p.m.	2	—	—	—	—	2
Placebo	a.m.	—	2	—	3	—	—
	p.m.	—	2	—	—	—	2

IVA = ivacaftor; LUM = lumacaftor; LUM/IVA = lumacaftor/ivacaftor; q12h = every 12 hours; qd = once daily.
Source: Clinical Study Reports for TRAFFIC[12] and TRANSPORT.[13]

3.2.4 Outcomes

a) Per cent predicted FEV_1

$ppFEV_1$ was calculated using the ratio of FEV_1 (L) to the predicted FEV_1 (L). The predicted FEV_1 was calculated using the Wang[34] standards for females aged 12 to 15 years and males aged 12 to 17 years. The Hankinson[35] standards were used for females aged 16 years and older and males aged 18 years and older.[12,13,31] At the time of this review, there is no established minimal clinically important difference (MCID) for absolute change in $ppFEV_1$ for CF patients.

Changes in $ppFEV_1$ were evaluated using absolute and relative changes:

- Absolute change in $ppFEV_1$: The pre-specified primary efficacy end point was the absolute change from baseline in $ppFEV_1$ using the average of weeks 16 and 24. Absolute change from baseline was calculated as post-baseline value minus baseline value.
- Relative change in $ppFEV_1$: A pre-specified key secondary efficacy end point calculated and expressed in percentages as 100 × (post-baseline value – baseline value)/baseline value.[12,13]

The manufacturer conducted a series of responder analyses for absolute and relative changes in $ppFEV_1$. Patients could be considered responders if they demonstrated an improvement of ≥ 3%, ≥ 5%, and ≥ 10% in average absolute change from baseline in $ppFEV_1$ at week 16 and week 24. A similar analysis was conducted for patients who demonstrated an improvement of ≥ 5% and ≥ 10% in average relative change from baseline in $ppFEV_1$ at week 16 and week 24. ≥ 5% improvement in average relative change from baseline in $ppFEV_1$ at week 16 and week 24 was a pre-specified key secondary end point.

b) Pulmonary exacerbations

Pulmonary exacerbations were defined as a change in antibiotic therapy (IV, inhaled, or oral) for any four or more of the following signs or symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in lung function by at least 10%; or radiographic changes indicative of pulmonary

infection. Changes in antibiotic therapy for sinopulmonary signs and/or symptoms were determined and documented by the study investigator at each study visit.[12,13] If at least four of the above-noted sinopulmonary signs and symptoms were present at the visit, the investigator completed a separate form within the case report form to determine the start and stop date of these events and whether they required hospitalization.

Several of the criteria for sinopulmonary signs and symptoms were measured objectively by the investigator alone (including temperature above 38°C, anorexia or weight loss, sinus pain or tenderness, change in physical examination of chest, decrease in pulmonary function by 10%, and radiographic changes indicative of pulmonary infection). Changes in sputum; new or increased hemoptysis; increase cough; increased dyspnea; malaise, fatigue, or lethargy; and change in sinus discharge were independently assessed by the investigator, or together with patient description, evaluated and reported by the investigator. There does not appear to have been an independent adjudication of pulmonary exacerbation events.

The following end points related to exacerbations were evaluated:[31]

- Number of pulmonary exacerbations from baseline to week 24 (key secondary end point)
- Time to first pulmonary exacerbation
- Incidence of having at least one pulmonary exacerbation
- Days with pulmonary exacerbations
- Pulmonary exacerbations requiring hospitalization
- Days hospitalized for pulmonary exacerbation
- Time to first hospitalization for pulmonary exacerbation
- Pulmonary exacerbations requiring IV antibiotics
- Days on IV antibiotic therapy for pulmonary exacerbation
- Time to first IV antibiotic therapy for pulmonary exacerbation.[31]

c) Body mass index, weight, and height

Both TRAFFIC and TRANSPORT evaluated changes from baseline in BMI, body weight, and height. For patients aged 12 to 20 years, these end points were adjusted for age and sex, and analyzed as BMI-for-age z score, weight-for-age z score, and height-for-age z score.[31] Absolute change from baseline in BMI was a pre-specified key secondary end point.

d) Cystic Fibrosis Questionnaire–Revised

The Cystic Fibrosis Questionnaire–Revised (CFQ-R) is a disease-specific instrument used to evaluate changes in respiratory symptoms, digestive symptoms, emotion, and health perception.[31] The respiratory domain of the CFQ-R includes items related to coughing, mucus, and ease of breathing. The respiratory domain of the CFQ-R scale is scored from 0 to 100 points, with higher scores indicating fewer respiratory symptoms.[31] A difference of at least four points in the respiratory domain score of the CFQ-R has been cited as the MCID. Separate versions of the CFQ-R have been created for adolescents and adults, parents and caregivers, children aged six to 11 years, and children aged 12 to 13 years.[31] The absolute change from baseline in the respiratory domain score of the CFQ-R at 24 weeks was a pre-specified key secondary end point in both the TRAFFIC and TRANSPORT studies.[12,13]

e) EQ-5D-3L

The EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire−3 Levels (EQ-5D-3L) is a generic utility measure of health-related quality of life used to evaluate the current health states of patients at least 12 years of age.[31] The EQ-5D-3L consists of two sections:

- The EQ-5D descriptive system consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (scored as no problems, some problems, or extreme problems). The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. The lowest possible overall score (corresponding to severe problems on all five attributes) is −0.109. Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. The MCID for the EQ-5D ranges from 0.033 to 0.074.[36] The validity and MCID of the EQ-5D have not been formally assessed in CF.
- The EQ visual analogue scale (VAS) captures patients' self-rated health on a VAS where the end points are labelled "best imaginable health state" (score of 100) and "worst imaginable health state" (score of 0).[37] The MCID for the EQ-5D VAS in CF patients is uncertain.

3.2.5 Statistical Analysis

a) Primary end point

Absolute changes from baseline in $ppFEV_1$ were calculated using a mixed-effects model for repeated measures (MMRM) approach. The model — including absolute change from baseline in $ppFEV_1$ as the dependent variable, and treatment, visit, and treatment-by-visit interaction as fixed effects, with adjustment for sex, age at baseline (< 18 versus ≥ 18 years), and $ppFEV_1$ at screening (< 70% versus ≥ 70%), and patient as a random effect — was used to test the difference between the LUM/IVA and placebo groups. Missing post-baseline values were not imputed for efficacy analyses conducted using the MMRM approach. The following sensitivity analyses of the primary end point were performed by the manufacturer to assess the robustness of the primary analysis:

- MMRM with on-treatment measurements only
- Analysis of covariance (ANCOVA) with multiple imputation (MI).

b) Secondary end points

TRAFFIC and TRANSPORT included the following five key secondary efficacy end points (all of which were included in the manufacturer's statistical testing hierarchy d)):

- Average relative change from baseline in $ppFEV_1$ at week 16 and 24
- Absolute change from baseline in BMI at week 24
- Absolute change from baseline in the CFQ-R–respiratory domain at week 24
- ≥ 5% increase in average relative change from baseline in $ppFEV_1$ at week 16 and 24
- Number of pulmonary exacerbations through week 24.

Other secondary and or additional efficacy end points of interest for this review were as follows:

- Absolute changes from baseline to 24 weeks in BMI z score, weight, weight z score, height, height z score, EQ-5D-3L
- Number of pulmonary exacerbations requiring hospitalizations or requiring IV antibiotics
- Time to first IV pulmonary exacerbation, pulmonary exacerbation requiring hospitalization, or pulmonary exacerbations requiring IV antibiotics.

The statistical evaluation of the continuous key and other secondary end points (e.g., $ppFEV_1$, BMI, CFQ-R, EQ-5D, weight, and height) were conducted using an MMRM model similar to that used for the

primary analysis, but with the addition of the baseline value for the end point of interest as a covariate. For number of pulmonary exacerbations (overall and those requiring IV antibiotics or hospitalization), the comparison between the LUM/IVA and placebo groups was conducted using regression analyses for a negative binomial distribution with sex, baseline age group (< 18 versus ≥ 18 years), and baseline $ppFEV_1$ severity at screening (< 70% versus ≥ 70%) as covariates. Time to first pulmonary exacerbation (any exacerbation and those requiring IV antibiotics or hospitalization) was analyzed using Cox regression. The manufacturer's model included a main effect for treatment, with covariates for sex, baseline age group (< 18 versus ≥ 18 years), and $ppFEV_1$ severity at screening (< 70% versus ≥ 70%). The responder analyses for improvements of ≥ 3%, ≥ 5%, and ≥ 10% in average absolute change from baseline in $ppFEV_1$ and ≥ 5% or ≥ 10% in average relative change from baseline in $ppFEV_1$ were conducted using a two-sided Cochran–Mantel–Haenszel test stratified by sex, age at baseline (< 18 versus ≥ 18 years), and $ppFEV_1$ at screening (< 70% versus ≥ 70%). Patients with a missing average absolute change from baseline in $ppFEV_1$ at weeks 16 and 24 were considered to be non-responders.

c) Power calculation

The manufacturer's sample size calculations were identical in both TRAFFIC and TRANSPORT. The sample size was based on absolute change from baseline in ppFEV1 at end point, with the following assumptions:

- A treatment difference of mean absolute change from baseline in $ppFEV_1$ of 5% between the active and placebo treatment groups, and a common standard deviation (SD) of 8%
- A 10% missing data or dropout rate
- A two-sided, two group, *t* test of equal means
- An alpha of 0.025 to address the multiplicity across the two active doses (a parallel gatekeeping approach with Bonferroni adjusted alpha levels) to ensure an overall type I error of 0.05.

A total sample size of 501 patients (167 per treatment group) had approximately 99% power to detect a treatment difference of 5% in absolute change in $ppFEV_1$between either dose of LUM/IVA compared with placebo.

d) Multiplicity adjustment

The overall type I error rate was controlled at 0.05 in both TRAFFIC and TRANSPORT using a Bonferroni correction (to adjust for multiple treatment groups) and a hierarchical testing procedure for the primary end point and the five key secondary end points. The testing hierarchy for primary and key secondary analyses was ordered as follows:[30]

- Absolute change from baseline in $ppFEV_1$
- Relative change from baseline in $ppFEV_1$
- Absolute change from baseline in BMI
- Absolute change from baseline in the CFQ-R–respiratory domain
- Threshold of ≥ 5% increase relative to baseline in $ppFEV_1$
- Number of pulmonary exacerbations.

Failure to demonstrate statistically significant differences stopped the statistical testing hierarchy at BMI in TRAFFIC (section c)) and at CFQ-R–respiratory domain in TRANSPORT (section d)).

All other end points, including subgroup and pooled analyses, were tested at an $\alpha = 0.025$ level without additional adjustment for multiplicity.

e) Analysis populations

In TRAFFIC and TRANSPORT, the evaluations of safety and efficacy end points were conducted using the following analysis sets:

- Full analysis set (FAS): The FAS was used for all efficacy analyses and consisted of all randomized patients who received at least one dose of study drug.
- Per-protocol set (PPS): The PPS was used for supportive analyses for primary and key secondary end points and consisted of all FAS patients without any of the following protocol violations:
  - Less than 80% compliance with study drug treatment
  - Not homozygous for the F508del-CFTR mutation
  - Failure to meet inclusion or exclusion criteria related to $ppFEV_1$; respiratory infection, pulmonary exacerbation, or changes in therapy for pulmonary disease within four weeks; organ or hematological transplantation; participation in an investigational drug study
  - Receipt of a prohibited medication that may have confounded efficacy results (as determined by case-by-case review of data)
  - Failure to provide informed consent.
- Safety set: The safety set was used for all safety analyses and consisted of all patients who received at least one dose of study drug.

f) Subgroup analyses

Subgroup analyses were conducted for the primary end point and all key secondary end points based on the following parameters: age (12 to < 18 years or ≥ 18 years), $ppFEV_1$ at screening (< 70% or ≥ 70% and < 40% or ≥ 40%), sex (male or female), region (North America, Europe, or Australia), *P. aeruginosa* status (positive or negative), use of inhaled antibiotics (yes or no), bronchodilators (yes or no; short-acting only, short-acting and long-acting, or long-acting only), inhaled hypertonic saline (yes or no), and inhaled corticosteroids (yes or no). In accordance with the CDR systematic review protocol, results are summarized for the following subgroups of interest: age (12 to < 18 years or ≥ 18 years), $ppFEV_1$ at screening (< 70% or ≥ 70% and < 40% or ≥ 40%).

g) Pooled analyses

The manufacturer conducted a pooled analysis of the data from the TRAFFIC and TRANSPORT studies as part of its Integrated Summary of Efficacy. The pooled analyses of efficacy end points were conducted in the same manner as the analyses in the individual studies, but using a pooled database of the study results (i.e., the analyses were conducted using patient-level data as opposed to study-level data).[38] A statistical testing hierarchy was not applied, and the treatment difference was considered statistically significant if $P \leq 0.0250$ (Bonferroni correction for multiple treatment groups).[31,38]

3.3 Patient Disposition

Patient disposition was similar in the both the TRAFFIC and TRANSPORT studies (Table 10). Discontinuation from the studies was greater in the LUM/IVA groups (5.5% to 8.0%) than in the placebo groups (2.2% to 2.7%) of both studies. This was primarily due to differences in withdrawals due to adverse events (WDAEs) in TRANSPORT (5.9% versus 1.1%). In TRAFFIC, there were also numerically more WDAEs in the LUM/IVA group than in the placebo group (3.3% versus 2.2%), but the difference in the overall discontinuation rate was also attributable to four LUM/IVA-treated patients who were withdrawn for other reasons (i.e., refusal of further dosing [n = 1], physician decision [n = 1], and determination that the patient did not actually meet the eligibility criteria of the study [n = 2]). The FASs of TRAFFIC and TRANSPORT included nearly all randomized patients (98% to 100% from the placebo groups and 97% to 99% from LUM/IVA groups).

TABLE 10: PATIENT DISPOSITION IN TRAFFIC AND TRANSPORT

Disposition, n (%)	TRAFFIC		TRANSPORT	
	Placebo	LUM/IVA	Placebo	LUM/IVA
Screened	720		726	
Randomized				
All treatment groups	559		563	
Groups of interest	187	187	187	189
Analysis sets				
Full analysis set	184	182	187	187
Per-protocol set	177	176	182	181
Safety set	184	182	187	187
Completed treatment	180 (97.8)	172 (94.5)	182 (97.3)	172 (92.0)
Discontinued treatment	4 (2.2)	10 (5.5)	5 (2.7)	15 (8.0)
Adverse event	4 (2.2)	6 (3.3)	2 (1.1)	11 (5.9)
Completed study	182 (98.9)	176 (96.7)	185 (98.9)	180 (96.3)
Discontinued study	2 (1.1)	6 (3.3)	2 (1.1)	7 (3.7)
Adverse event	2 (1.1)	2 (1.1)	1 (0.5)	2 (1.1)
Withdrawal of consent	0 (0.0)	2 (1.1)	1 (0.5)	2 (1.1)
Other, non-compliance	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Physician decision	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (0.5)	0 (0.0)	2 (1.1)

LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients; q12h = every 12 hours.
Source: Adapted from Common Technical Document section 2.7.3[31] and Clinical Study Reports for TRAFFIC[12] and TRANSPORT[13]

3.4 Exposure to Study Treatments

Patient exposure to the study drugs in TRAFFIC and TRANSPORT is summarized in Table 11. The mean treatment duration was similar in the LUM/IVA groups (162.8 days in TRAFFIC and 160.6 days in TRANSPORT) and the placebo (166.4 days in TRAFFIC and 164.5 days in TRANSPORT) groups of both studies.

TABLE 11: SUMMARY OF EXPOSURE TO STUDY DRUGS IN TRAFFIC AND TRANSPORT

Statistic	TRAFFIC		TRANSPORT	
	Placebo (N = 184)	LUM/IVA (N = 182)	Placebo (N = 187)	LUM/IVA (N = 187)
Total exposure, patient years	83.8	81.1	84.2	82.2
Exposure duration, days				
Mean (SD)	166.4 (13.19)	162.8 (23.64)	164.5 (20.88)	160.6 (31.26)
Median (range)	168.0 (32, 179)	168.0 (2, 178)	168.0 (7, 181)	168.0 (1, 182)
Exposure classification, n (%)				
> 0 to ≤ 2 weeks	0 (0.0)	1 (0.5)	2 (1.1)	5 (2.7)
> 2 to ≤ 4 weeks	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
> 4 to ≤ 8 weeks	1 (0.5)	4 (2.2)	0 (0.0)	2 (1.1)
> 8 to ≤ 16 weeks	1 (0.5)	2 (1.1)	1 (0.5)	2 (1.1)
> 16 to ≤ 24 weeks	150 (81.5)	145 (79.7)	141 (75.4)	145 (77.5)
> 24 weeks	32 (17.4)	30 (16.5)	42 (22.5)	33 (17.6)

LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients; q12h = every 12 hours; SD = standard deviation.
Source: Common Technical Document section 2.7.3.[31]

3.5 Critical Appraisal

3.5.1 Internal Validity

Health Canada reviewers noted that the clinical development program for LUM/IVA was consistent with expectations for a disease with the incidence of CF due to F508del-CFTR mutations.[2] TRAFFIC and TRANSPORT were designed and conducted in accordance with guidance and recommendations from regulatory authorities.[39] Allocation was concealed using an interactive Web response system to assign participants to the treatment groups. Randomization was stratified by relevant demographic (i.e., age and sex) and baseline characteristics (i.e., ppFEV$_1$). The treatment groups were generally well balanced with respect to key baseline and demographic characteristics. Subgroup analyses were pre-specified in the study protocols and investigated treatment effects based on relevant patient characteristics. Statistical tests for subgroup analyses were conducted without adjustment for multiple comparisons.

In TRAFFIC, the manufacturer reported that a greater proportion of patients in the placebo group received dornase alfa before the first dose of study drug (73.4%) compared with LUM/IVA (67.6%). This could potentially bias the treatment effect against LUM/IVA, as the increased use of dornase alfa, a mucolytic drug, could favour placebo participants for respiratory end points.

The proportion of study participants who were receiving inhaled antibiotics at baseline was greater in the placebo groups (66.3% to 72.7%) compared with the LUM/IVA groups (59.9% to 62.1%) in both TRAFFIC and TRANSPORT. The clinical expert consulted for the review agreed that this imbalance in baseline usage of antibiotics could potentially influence a patient's risk of experiencing a pulmonary exacerbation, but was uncertain as to the magnitude of the effect in TRAFFIC and TRANSPORT. The potential bias associated with this imbalance on outcomes including pulmonary exacerbations was also considered by reviewers for the European Medicines Agency (EMA), who determined that a definitive conclusion could not be made. They noted that it is unclear if a greater usage of antibiotics at baseline would be correlated with an increased risk of an exacerbation (e.g., the antibiotics are provided to those who are at the greatest risk)

or a decreased risk of an exacerbation (e.g., the concomitant use of antibiotics provides a protective effect that would lower the risk).[5]

Study treatments were administered in a double-blind manner, with all groups issued the same number of tablets each day. The active and placebo tablets were identical in appearance. LUM/IVA was associated with an increase in some gastrointestinal and respiratory adverse events; however, the clinical expert consulted by CDR noted that the differences were unlikely to significantly compromise blinding of the studies.

Patient disposition was thoroughly documented and well reported. Approximately 95% of patients in each study completed the 24-week double-blind treatment period. The full analysis sets of TRAFFIC and TRANSPORT included nearly all randomized patients, but were not a true intention-to-treat (ITT) data set. FDA statistical reviewers noted that the amount of missing data in the two studies was minimal and not a concern.[40] Compliance with the study treatments was evaluated by counting the number of study drugs at each visit and was reported to be > 98% across all treatment groups in both the TRAFFIC and TRANSPORT studies. In accordance with the study protocol, the use of concomitant medications remained stable throughout the treatment period for all treatment groups. The only documented exception is the lower usage of IV antibiotics for pulmonary exacerbations, a pre-specified end point, during the trials in the LUM/IVA groups compared with the placebo groups (Table 12).

There are no globally accepted definitions for pulmonary exacerbations in CF patients.[5] The definitions used in the TRAFFIC and TRANSPORT studies were considered to be appropriate by regulatory authorities and the clinical expert consulted by CDR. There does not appear to have been an independent adjudication of pulmonary exacerbation events.

Identical statistical power calculations were reported for both trials and a sufficient number of patients were enrolled and completed the studies. The number of withdrawals from the trials was below the 10% proportion assumed in the manufacturer's statistical power calculation,[31] providing additional power to detect differences between the two groups.[5] The FDA statistical reviewer noted that the pivotal trials were powered to detect differences in absolute $ppFEV_1$ as small as 1.65%; therefore, statistical significance for the primary end point alone would be insufficient to conclude that treatment with LUM/IVA is clinically beneficial.[40,41] They noted that a mean absolute change from baseline in $ppFEV_1$ of 1.7% in a phase 2 study (DISCOVER; N = 140)[42,43] of ivacaftor monotherapy in patients who were homozygous for the F508del mutation was transient and not sustained and was not considered to be a clinically meaningful treatment effect.[40]

Multiplicity adjustment (i.e., Bonferroni correction for multiple treatment groups) and hierarchical testing were used to control the overall type I error rate at 0.05 for the primary and a limited number of key secondary end points. Failure to demonstrate statistically significant differences stopped the statistical testing hierarchy at BMI in TRAFFIC and at CFQ-R–respiratory domain in TRANSPORT; however, the manufacturer continued to calculate and report *P* values for the remaining key secondary end points (i.e., nominal *P* values were considered to be descriptive).[40] Due to the failure of the hierarchy, results for the following key secondary end points were not statistically significant: differences in the number of pulmonary exacerbations and differences in the proportion of patients who demonstrated an improvement of ≥ 5% in relative change from baseline in $ppFEV_1$. Statistical analyses for the additional secondary end points, subgroup analyses, and the pooled analyses were conducted without adjustment for multiplicity; therefore, the findings should be considered exploratory.

3.5.2 External Validity

The diagnostic criteria used in the screening process for TRAFFIC and TRANSPORT were consistent with Canadian clinical practice for identifying patients with CF who are homozygous for the F508del-CFTR mutation. CF patients with more severe lung disease (e.g., $ppFEV_1$ < 40% at screening) or a normal $ppFEV_1$ at screening (≥ 90%) were excluded from the studies; therefore, the results of the included studies are primarily applicable to patients with moderate (i.e., FEV_1 40% to 69%) to mild (i.e., FEV_1 70% to 89%) lung disease. The manufacturer reported that this population was selected because it was considered to be the most likely patient group able to show an improvement in lung function in a clinical trial, based on their experience with ivacaftor and with other therapies targeting CF lung disease.[31] However, it should be noted that the trials enrolled a total of 81 patients with a $ppFEV_1$ < 40% at baseline. These patients with lower lung function would have satisfied the study inclusion criteria in the screening phase, then would have demonstrated a $ppFEV_1$ < 40% at their baseline evaluation. The data for this small subgroup of patients can provide some preliminary information on the safety and efficacy of LUM/IVA in patients with more severe lung deterioration, as more robust clinical data are currently being collected in an open-label, phase 3b, clinical study to evaluate LUM/IVA in CF patients who are homozygous for the F508del-CFTR mutation and are suffering from advanced lung disease (i.e., $ppFEV_1$ < 40%).[4]

A majority of the participants in TRAFFIC and TRANSPORT were from North America (52.6% and 62.4%, respectively). The study populations consisted of white patients almost exclusively (98.2% in TRAFFIC and 99.1% in TRANSPORT), which is reflective of the majority of patients who would be eligible for treatment with LUM/IVA, although the percentage is slightly higher than the proportion reported for the overall CF population in Canada (92% in 2013).[3]

The proportion of patients in TRAFFIC and TRANSPORT who had mild disease (64.3%) or moderate disease (26.6%) does not appear to reflect the distribution of FEV_1 categories for the overall adult Canadian CF population, where it has been reported that 27% and 38% have mild and moderate disease, respectively.[3] Reviewers for the EMA indicated that the study populations were generalizable to the indicated population; however, data on patients with rapidly progressive disease and patients who experience a greater number of exacerbations appear to be under-represented in the pivotal studies. Efficacy data for such patients would be beneficial and are likely to be obtained in the longer-term follow-up studies.[5] Reviewers for the EMA commented that the rate of decline of $ppFEV_1$ in the trial populations appeared to be slower than expected, based on European registry data.[5] In addition, the deterioration in $ppFEV_1$ in the placebo group was not consistent across the TRAFFIC and TRANSPORT (–0.73% and –0.02% at week 24, respectively). The clinical expert consulted by CDR noted that the deterioration in $ppFEV_1$ is often reduced in CF clinical trial settings, as a result of trial protocols and/or Hawthorne effect.

The Cystic Fibrosis Foundation clinical practice guidelines recommend that adult women and men (≥ 20 years of age) maintain a BMI at or above 22 kg/m^2 and 23 kg/m^2, respectively. Baseline BMI in the pivotal studies was 21.25 kg/m^2 and 21.10 kg/m^2, which are slightly below the estimated national median BMI for adult CF patients (22.1 kg/m^2) in Canada. The clinical expert noted that this may be attributable to the greater emphasis that is placed on nutritional status in Canadian CF clinics.

TRAFFIC and TRANSPORT excluded patients with a history of colonization with *B. cenocepacia*, *B. dolosa*, and/or *M. abscessus*. The Canadian Cystic Fibrosis Registry indicated that approximately 5% of CF patients in Canada are infected with *Burkholderia cepacia* complex species (88.2% of whom are adults).[3] The clinical expert consulted by CDR noted that the exclusion of such patients does not significantly

lower the generalizability of the study results, given that these patients represent a small minority of those who could be eligible for LUM/IVA and that the clinical management of such patients is more complex and variable than those without *B. cepacia* infection. The clinical expert noted that the exclusion criteria of TRAFFIC and TRANSPORT were less restrictive than many CF clinical trials, as they permitted enrolment of patients with some *B. cepacia* complex species.

The proportion of patients who were positive for *P. aeruginosa* was 74.4% and 77.5% in the placebo and LUM/IVA groups, respectively. This is greater than the infection rates reported in the overall Canadian CF population (i.e., 43% in 2013). The expert consulted by CDR noted that infection with *P. aeruginosa* in Canada is treated with the use of inhaled antibiotics; therefore, the rates of inhaled antibiotic usage are slightly lower than would be anticipated in a similar Canadian population (i.e., 74.1% infected with *P. aeruginosa* but only 64.5% with exposure to inhaled antibiotics).[16] However, the clinical expert consulted by CDR noted that this difference is unlikely to materially reduce the generalizability of the study results.

The pivotal studies excluded patients who had a respiratory infection, pulmonary exacerbation, or changes in their therapy for pulmonary disease within four weeks before the first dose of study drug. The clinical expert consulted by CDR noted that, due to the potential for LUM/IVA to cause respiratory adverse events during the initiation of treatment, clinicians would not typically start a patient on LUM/IVA during or shortly after a pulmonary exacerbation.

Similar to the pivotal studies that were conducted for the use of ivacaftor monotherapy in the treatment of CF patients with gating mutations (i.e., STRIVE, ENVISION, KONNECTION, and KONDUCT),[44-47] the use of placebo as the comparator is appropriate, as LUM/IVA is a novel treatment for CF patients with F508del-CFTR mutations. Both TRAFFIC and TRANSPORT compared the addition of LUM/IVA or placebo to ongoing standard CF-management therapies, which is reflective of how LUM/IVA would be administered in clinical practice. In general, the background therapies that were reported at baseline in TRAFFIC and TRANSPORT were consistent with those used in Canadian clinical practice. However, the proportion of patients using dornase alfa in the studies likely exceeds the proportion using this product in Canadian clinical practice. It should be noted that, in contrast to the pivotal studies for ivacaftor (i.e., STRIVE, ENVISION, and KONNECTION),[44-46] patients in TRAFFIC and TRANSPORT were permitted to use inhaled hypertonic saline. Inhaled hypertonic saline is commonly used in Canadian clinical practice; therefore, this feature of TRAFFIC and TRANSPORT improves the generalizability of the studies compared with the pivotal studies of ivacaftor.

TRAFFIC and TRANSPORT evaluated the impact of LUM/IVA on a range of different outcomes that are considered to be important in the management of CF. These included respiratory function (i.e., $ppFEV_1$), nutritional status and growth (e.g., weight, height, and BMI), health-related quality of life (CFQ-R and EQ-5D-3L), and clinical events (e.g., pulmonary exacerbations). Spirometry measurements were standardized and performed according to the American Thoracic Society Guidelines (e.g., pre-bronchodilator and before dosing).[48] Changes in the primary end point (i.e., absolute change in $ppFEV_1$) were evaluated after six months of treatment with the study drugs. This end point and time point are aligned with guidance from the EMA on the clinical development of drugs for the treatment of CF.[39] In general, the other end points that were evaluated in the pivotal studies were also aligned with recommendations from the EMA, with the exception of longer-term safety, which was primarily evaluated in the PROGRESS extension study.[5]

The 24-week study treatment periods were sufficient for observing treatment differences in the primary end point and many of the secondary end points in the pivotal studies; however, the duration was too short to observe whether or not treatment with LUM/IVA has the potential to modify the course of disease for CF patients with F508del-CFTR mutations.[30] Twenty-four-week data from the PROGRESS extension study (i.e., 48 weeks of LUM/IVA treatment) suggested that patients treated with LUM/IVA maintained the improvements that were observed in TRAFFIC and TRANSPORT; however, the relatively short duration of follow-up at the time of analysis for a chronic condition (i.e., an additional 24 weeks), the absence of a control group, and the uncertainty regarding the baseline values used in the interim analysis preclude any conclusions regarding the long-term effectiveness of LUM/IVA.

The primary end point of TRAFFIC and TRANSPORT was evaluated using the average effect at week 16 and at week 24, rather than just the $ppFEV_1$ at week 24. The manufacturer elected to use the average of weeks 16 and 24 to reduce variability compared with using a single measurement at week 24 alone.[12,13] However, the results were similar when the end point was analyzed using only the week 24 data, as required by the EMA.[5] The clinical experts consulted by CDR and NICE[49] both indicated that using the average of multiple time points is a method of reducing variability when evaluating changes in $ppFEV_1$.

EQ-5D index scores at baseline were relatively high, with approximately half of all patients reporting a score of 1.0 (i.e., perfect health) at baseline. This creates a ceiling effect, making it challenging to observe potential differences between the active and placebo treatment groups. In addition, there are no established MCIDs for the EQ-5D index scores and VAS scores in CF patients.

As is common in clinical trial settings, patients enrolled in TRAFFIC and TRANSPORT received extensive contact with health professionals over the 28-week study period (i.e., seven clinic visits and three phone contacts). This level of contact is not reflective of routine care for CF patients with relatively stable disease. Due to the need to ensure that all three treatment groups received the same number of tablets, patients in the TRAFFIC and TRANSPORT studies underwent a more complicated dosage regimen than would be required for typical administration of LUM/IVA. In clinical practice, patients using the typical recommended dosage of LUM/IVA would take two tablets every 12 hours (i.e., four tablets per day). In contrast, in TRAFFIC and TRANSPORT, patients would take five tablets in the morning and four tablets in the afternoon (i.e., nine tablets per day). Nevertheless, as noted above, compliance with study treatments was very high throughout the double-blind treatment period. The clinical expert consulted by CDR noted that the level of compliance observed in the TRAFFIC and TRANSPORT studies is not reflective of typical patient adherence in Canada, where compliance with treatments, including orally administered treatments, is considerably lower.[50]

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (Section 2.2, Table 5) are reported below. See APPENDIX 4: DETAILED OUTCOME DATA for additional efficacy data.

3.6.1 FEV_1

a) Absolute change in $ppFEV_1$

Treatment with LUM/IVA was associated with a statistically significant increase from baseline in $ppFEV_1$ compared with placebo in the FAS of both TRAFFIC (2.60%; 95% confidence interval [CI], 1.18% to 4.01%) and TRANSPORT (3.00%; 95% CI, 1.56% to 4.44%) (

Figure 3). The result in the pooled analysis was 2.81% (95% CI, 1.80 to 3.82). As shown in Figure 4A, improvements in $ppFEV_1$ with LUM/IVA were observed at the time of the first post-baseline assessment

(i.e., day 15) in both TRAFFIC and TRANSPORT and were statistically significant improvements in $ppFEV_1$ at all time points (Table 23). Results of the sensitivity analyses using MMRM with on-treatment measurements only and ANCOVA with MI were consistent with the result of the primary analysis (Table 25).

As shown in Figure 5, results for $ppFEV_1$ were generally consistent across subgroup analyses based on age (12 to < 18 years or ≥ 18 years), $ppFEV_1$ at screening (< 70% or ≥ 70%), and $ppFEV_1$ baseline (< 40% or ≥ 40%); however, there is considerable uncertainty in subgroup analyses with small sample sizes, such as age 12 to 18 years, and $ppFEV_1$ ≥ 70% at screening and < 40% at baseline.

b) Relative change in $ppFEV_1$

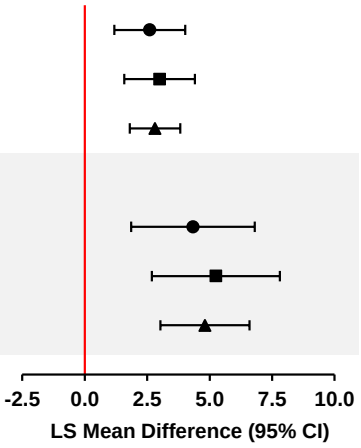
Treatment with LUM/IVA was associated with a statistically improvement in relative change from baseline in $ppFEV_1$ in both studies. The relative treatment differences in $ppFEV_1$ were 4.33% (95% CI, 1.86 to 6.80) and 5.25% (95% CI, 2.69 to 7.81) in TRAFFIC and TRANSPORT, respectively (

Figure 3). The result in the pooled analysis was 4.81% (95% CI, 3.03 to 6.59). Similar to results for absolute change in $ppFEV_1$, statistically significant differences in relative change in $ppFEV_1$ were observed at all post-baseline study visits (Table 23).

As shown in Table 24, results for $ppFEV_1$ were generally consistent across subgroup analyses based on age, $ppFEV_1$ at screening, and $ppFEV_1$ at baseline. Similar to absolute change in $ppFEV_1$, there is uncertainty in the results for subgroup analyses with small sample sizes.

FIGURE 3: ABSOLUTE AND RELATIVE CHANGE IN $ppFEV_1$ FROM TRAFFIC AND TRANSPORT

Study	LS Mean Change (SE)		LUM/IVA vs. Placebo	
	Placebo	LUM/IVA	LSMD (95% CI)	P value
Absolute change from baseline in $ppFEV_1$				
TRAFFIC	−0.44 (0.524)	2.16 (0.530)	2.60% (1.18 to 4.01)	0.0003
TRANSPORT	−0.15 (0.539)	2.85 (0.540)	3.00% (1.56 to 4.44)	<0.0001
Pooled	−0.32 (0.376)	2.49 (0.379)	2.81% (1.80 to 3.82)	<0.0001
Relative change from baseline in $ppFEV_1$				
TRAFFIC	−0.34 (0.913)	3.99 (0.923)	4.33% (1.86 to 6.80)	0.0006
TRANSPORT	0.00 (0.960)	5.25 (0.961)	5.25% (2.69 to 7.81)	<0.0001
Pooled	−0.17 (0.662)	4.64 (0.666)	4.81% (3.03 to 6.59)	<0.0001

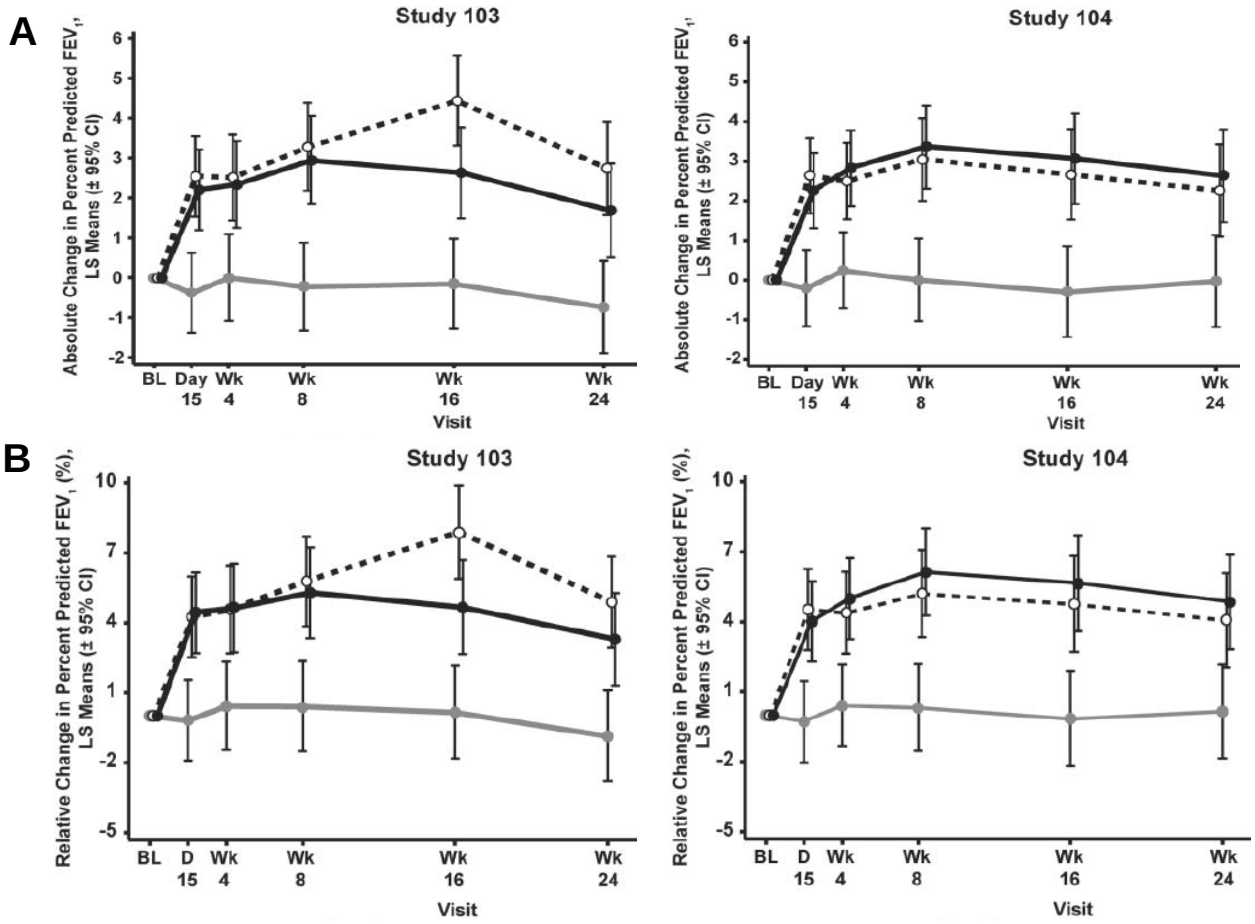


CI = confidence interval; LS = least squares; LSMD = least squares mean difference; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; MMRM = mixed-effects model for repeated measures; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; q12h = every 12 hours; SE = standard error.

Notes:

- MMRM model included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at baseline (< 18 versus ≥ 18 years), and $ppFEV_1$ at screening (< 70% versus ≥ 70%).[12,13]
- Figure shows the absolute and relative change from baseline in $ppFEV_1$ for LUM 400 mg q12h + IVA 250 mg q12h versus placebo for the full analysis sets of TRAFFIC (●), TRANSPORT (▲), and the pooled analysis conducted by the manufacturer (■).

FIGURE 4: ABSOLUTE (A) AND RELATIVE (B) CHANGE IN ppFEV$_1$ FROM TRAFFIC AND TRANSPORT



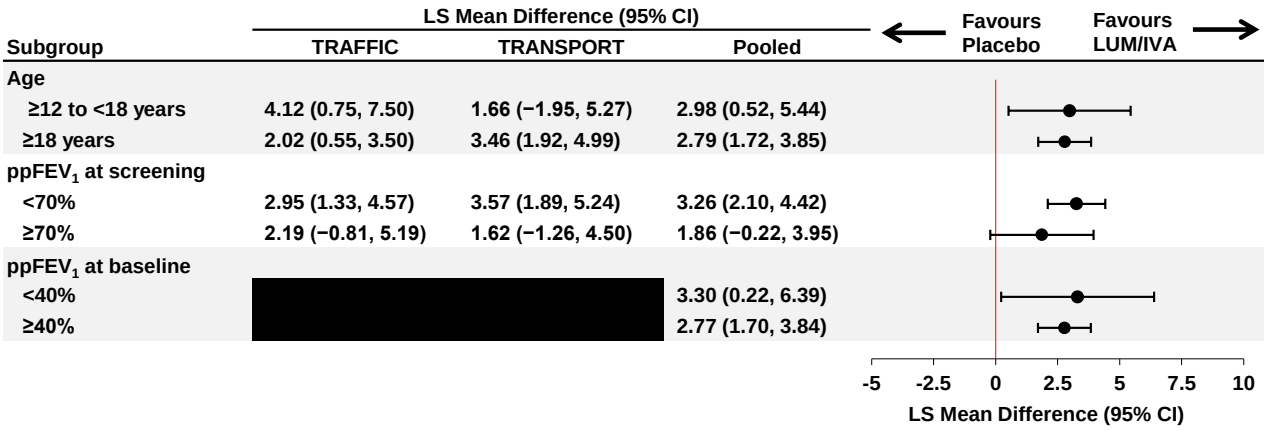
BL = baseline; CI = confidence interval; D = day; FEV_1 = forced expiratory volume in 1 second; LS = least squares; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; MMRM = mixed-effects model for repeated measures; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; q12h = every 12 hours; qd = once daily; Study 103 = TRAFFIC; Study 104 = TRANSPORT; wk = week.

Notes:

- MMRM model included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at baseline (< 18 versus ≥ 18 years), and $ppFEV_1$ severity at screening (< 70% versus ≥ 70%).[12,13]
- Figure shows the absolute (A) and relative (B) change from baseline in $ppFEV_1$ for LUM 600 mg qd + IVA 250 mg q12h (○), LUM 400 mg q12h + IVA 250 mg q12h (●), and placebo (●).

Source: Clinical Study Reports for TRAFFIC[12] and TRANSPORT.[13]

FIGURE 5: SUBGROUP ANALYSES FOR ABSOLUTE CHANGE IN PPFEV$_1$



CI = confidence interval; LS = least squares; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; MMRM = mixed-effects model for repeated measures; ppFEV$_1$ = per cent predicted forced expiratory volume in 1 second; q12h = every 12 hours.

Notes:

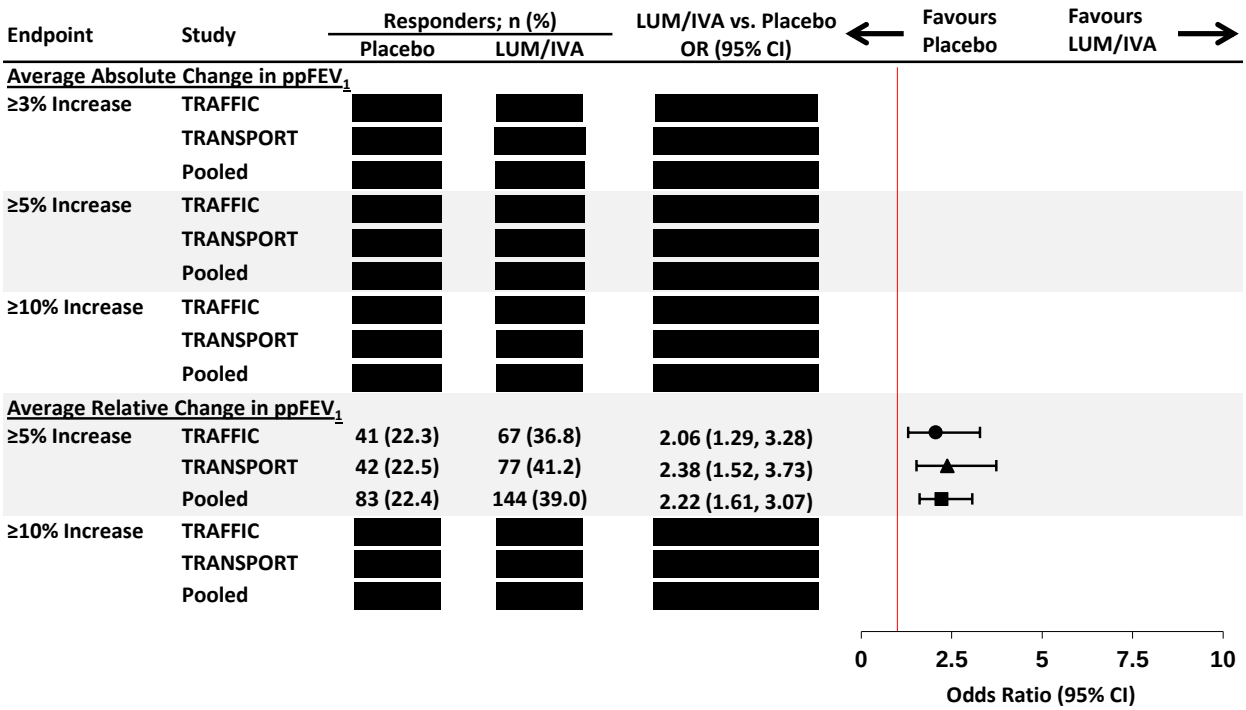
- MMRM model included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at baseline (< 18 versus ≥ 18 years), and ppFEV$_1$ severity at screening (< 70% versus ≥ 70%).[12,13]
- Figure shows pooled results for the difference in absolute change from baseline in ppFEV$_1$ for LUM 400 mg q12h + IVA 250 mg q12h versus placebo.

c) FEV$_1$ responder analysis

The proportion of patients who demonstrated an improvement of ≥ 5% in relative change from baseline in ppFEV$_1$ was a key secondary end point of the included studies and, therefore, was included in the manufacturer's pre-specified statistical testing hierarchy. Statistical significance could not be concluded for differences in this end point, as the statistical testing hierarchy was stopped prior to this outcome. All other responder analyses (including the analyses based on both absolute and relative changes) were secondary end points and were outside of the pre-specified statistical testing strategy, which means the analyses are considered to be exploratory, and the results should be interpreted with caution. Similarly, the statistical tests for the pooled analyses of the different responder analyses were conducted without adjustment for multiplicity and should be interpreted with caution.

Across both studies, a greater proportion of LUM/IVA-treated patients achieved improvements in ppFEV$_1$ of at least 3%, 5%, or 10% based on absolute changes from baseline and improvements of 5% and 10% based on relative changes from baseline. As shown in Figure 6, less than half of LUM/IVA-treated patients demonstrated an absolute improvement of ≥ 3% in ppFEV$_1$ ([redacted] and [redacted] in TRAFFIC and TRANSPORT, respectively), fewer than one-third achieved an absolute increase ≥ 5% in ppFEV$_1$ ([redacted] and [redacted] in TRAFFIC and TRANSPORT, respectively), and only a small minority achieved an increase of ≥ 10% ([redacted] and [redacted] in TRAFFIC and TRANSPORT, respectively). The pooled analysis demonstrated that LUM/IVA was associated with increased odds of achieving a response compared with placebo (odds ratios of [redacted] for ≥ 3% increase, [redacted] for ≥ 5% increase, and [redacted] for ≥ 10% increase).

FIGURE 6: RESPONDER ANALYSIS OF AVERAGE CHANGE FROM BASELINE IN $ppFEV_1$



CI = confidence interval; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients with events; OR = odds ratio; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second.

Notes:

- Cochran–Mantel–Haenszel test stratified by sex (male versus female), age group at baseline (< 18 versus ≥ 18 years), and $ppFEV_1$ severity at screening (< 70% versus ≥ 70%).[12,13]
- Figure shows the ORs for demonstrating improvement of at least 3%, 5%, or 10% in absolute change from baseline in $ppFEV_1$ or at least 5% or 10% improvement in relative change in $ppFEV_1$ in TRAFFIC (●), TRANSPORT (▲), and the pooled analysis conducted by the manufacturer (■).

[a] The proportion of patients with a relative increase of at least 5% was a key secondary end point; therefore, the statistical testing hierarchy was enforced for this end point and no conclusions with respect to statistical significance for this end point can be made.

3.6.2 Pulmonary Exacerbations

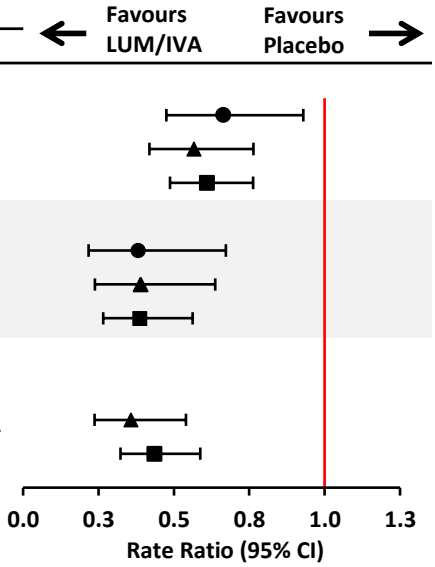
Difference in the number of pulmonary exacerbations was a key secondary end point of the included studies and, therefore, was included in the manufacturer's pre-specified statistical testing hierarchy. Statistical significance could not be concluded for differences in the number of pulmonary exacerbations, as the statistical testing hierarchy was stopped prior to this outcome. All other end points related to pulmonary exacerbations (including time-to-event end points) were secondary or additional end points and were outside of the pre-specified statistical testing strategy, which means the analyses are considered to be exploratory, and the results should be interpreted with caution. Similarly, the statistical tests for the pooled analyses of the different pulmonary exacerbation end points were conducted without adjustment for multiplicity and should be interpreted with caution.

In both TRAFFIC and TRANSPORT, treatment with LUM/IVA was associated with a lower rate of the pulmonary exacerbations compared with placebo (rate ratios were 0.66 [95% CI, 0.47 to 0.93] and 0.57 [95% CI, 0.42 to 0.76], respectively). Similarly, treatment with LUM/IVA was associated with lower rates

of the following pulmonary exacerbations requiring hospitalization and pulmonary exacerbations requiring IV antibiotic therapy (Figure 7). Hazard ratios for the above-noted end points demonstrated a favourable treatment for LUM/IVA compared with placebo (Table 12). For all end points related to pulmonary exacerbations, the results demonstrated numerical or statistically significant differences in favour of LUM/IVA.

FIGURE 7: RISK OF PULMONARY EXACERBATIONS IN TRAFFIC AND TRANSPORT

Study	Events (event rate/year)		LUM/IVA vs. Placebo	
	Placebo	LUM/IVA	Rate Ratio (95% CI)	P value
Any PEx				
TRAFFIC	112 (1.07)	73 (0.71)	0.66 (0.47 to 0.93)	0.0169[a]
TRANSPORT	139 (1.18)	79 (0.67)	0.57 (0.42 to 0.76)	0.0002[a]
Pooled	251 (1.14)	152 (0.70)	0.61 (0.49 to 0.76)	<0.0001
PEx requiring hospitalization				
TRAFFIC	46 (0.36)	17 (0.14)	0.38 (0.22 to 0.67)	0.0008
TRANSPORT	59 (0.46)	23 (0.18)	0.39 (0.24 to 0.64)	0.0002
Pooled	105 (0.45)	40 (0.17)	0.39 (0.26 to 0.56)	<0.0001
PEx requiring IV antibiotics				
TRAFFIC	62 (NA)	33 (NA)	No estimate	0.0050
TRANSPORT	87 (0.64)	31 (0.23)	0.36 (0.24 to 0.54)	<0.0001
Pooled	149 (0.58)	64 (0.25)	0.44 (0.32 to 0.59)	<0.0001



CI = confidence interval; IV = intravenous; LUM/IVA = lumacaftor/ivacaftor; PEx = pulmonary exacerbation; ppFEV1 = per cent predicted forced expiratory volume in 1 second; vs. = versus.

Notes:

– Treatment comparison was conducted using regression analysis for a negative binomial distribution with sex (male versus female), age group at baseline (< 18 versus ≥ 18 years), and ppFEV$_1$ at screening (< 70% versus ≥ 70%) as covariates with the logarithm of time on study as the offset.[12,13]
– Figure shows rate ratios for LUM/IVA versus placebo for pulmonary exacerbations in TRAFFIC (●), TRANSPORT (▲), and a pooled analysis conducted by the manufacturer (■).

[a] The number of pulmonary exacerbations was a key secondary end point; therefore, the statistical testing hierarchy was enforced for this end point. Although the *P* values are below 0.025, the manufacturer did not consider the results to be statistically significant.

TABLE 12: TIME TO FIRST PULMONARY EXACERBATION

Endpoints	TRAFFIC		TRANSPORT	
	Placebo	LUM/IVA	Placebo	LUM/IVA
Time to first pulmonary exacerbation				
Patients with event, n (%)	73 (39.7)	55 (30.2)	88 (47.1)	54 (28.9)
Hazard ratio[a]	0.691 (95% CI, NR)		0.533 (95% CI, NR)	
P value	0.0385		0.0003	
Time to first hospitalization for pulmonary exacerbation				
Patients with event, n (%)	39 (21.2)	17 (9.3)	48 (25.7)	20 (10.7)
Hazard ratio[a]	0.401 (95% CI, NR)		0.368 (95% CI, NR)	
P value	0.0017		0.0002	
Time to first pulmonary exacerbations requiring IV antibiotic therapy				
Patients with event, n (%)	51 (27.7)	28 (15.4)	64 (34.2)	26 (13.9)
Hazard ratio[a]	0.504 (95% CI, NR)		0.335 (95% CI, NR)	
P value	0.0036		< 0.0001	

CI = confidence interval; IV = intravenous; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients with events; NR = not reported; q12h = every 12 hours.

[a] Hazard ratio and *P* value were calculated using a Cox proportional hazard regression analysis with adjustment for sex, age group (< 18 versus ≥ 18 years), and ppFEV$_1$ at screening (< 70% versus ≥ 70%).[12,13]

Source: Clinical Study Reports for TRAFFIC[12] and TRANSPORT.[13]

3.6.3 Body Mass Index

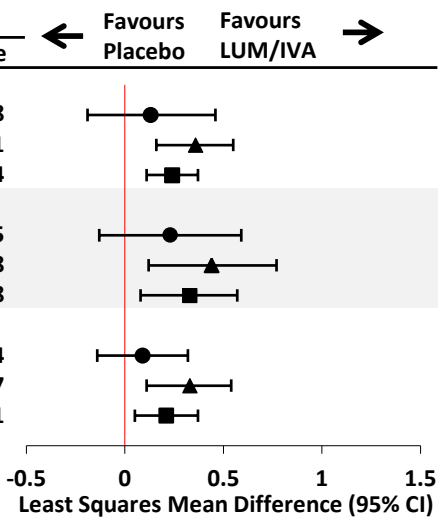
Change from baseline in BMI was a key secondary end point of the included studies and, therefore, was included in the manufacturer's pre-specified statistical testing hierarchy. However, change from baseline in BMI z score and the subgroup analyses for BMI were outside of the pre-specified statistical testing strategy, which means the analyses are considered to be exploratory, and the results should be interpreted with caution. Similarly, the statistical testing for the pooled analysis for change from baseline in BMI was conducted without adjustment for multiplicity and should be interpreted with caution.

Results for change from baseline in BMI were inconsistent across the TRAFFIC and TRANSPORT studies (Figure 8 and Table 13). In TRANSPORT, treatment with LUM/IVA was associated with statistically significant improvements in BMI (0.36 kg/m^2; 95% CI, 0.17 to 0.54) and BMI z score (0.222; 95% CI, 0.096 to 0.347) compared with placebo. In contrast, LUM/IVA failed to demonstrate a statistically significant difference for these end points in TRAFFIC (stopping the statistical testing hierarchy). The difference between LUM/IVA and placebo was statistically significant in the pooled analysis (0.24 kg/m^2 [95% CI, 0.11 to 0.37]; *P* = 0.0004). Results were consistent in subgroup analyses conducted for patients who were aged 12 to < 18 years and those who were older than 18 years of age.

As shown in Figure 9 and Table 14, treatment with LUM/IVA was associated with a statistically significant improvement in BMI z score compared with placebo in TRANSPORT (0.222; 95% CI, 0.096 to 0.347) and in the pooled analysis ([redacted]).

FIGURE 8: CHANGE FROM BASELINE IN BODY MASS INDEX

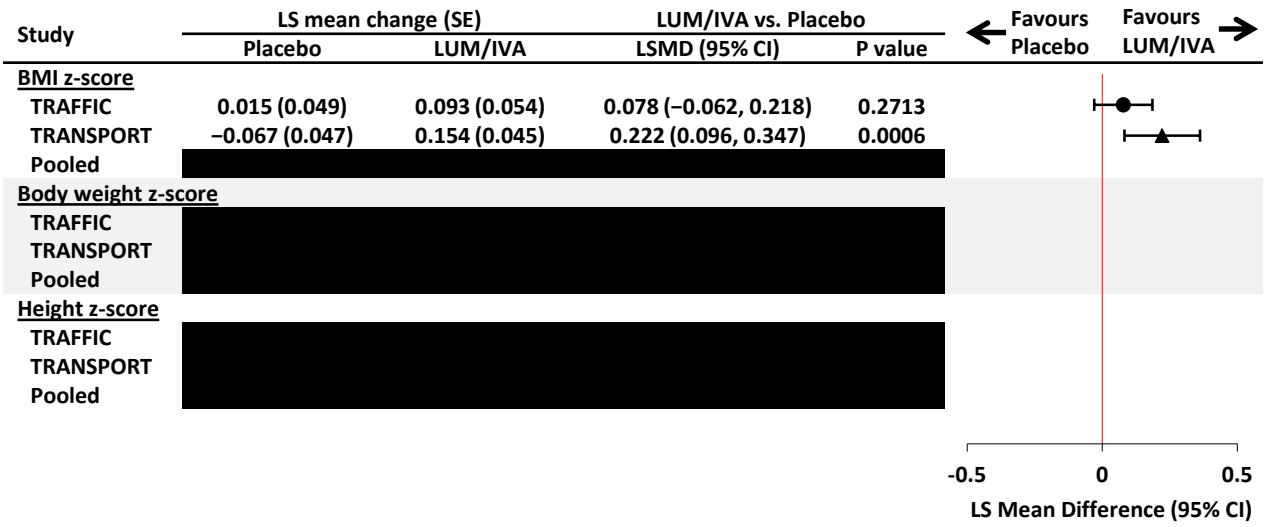
Study	LS mean change (SE)		LUM/IVA vs. Placebo	
	Placebo	LUM/IVA	LSMD (95% CI)	P value
BMI				
TRAFFIC	0.19 (0.070)	0.32 (0.071)	0.13 (−0.07, 0.32)	0.1938
TRANSPORT	0.07 (0.066)	0.43 (0.066)	0.36 (0.17, 0.54)	0.0001
Pooled	0.13 (0.048)	0.37 (0.048)	0.24 (0.11, 0.37)	0.0004
BMI (12 to 18 years)				
TRAFFIC	0.41 (0.128)	0.64 (0.130)	0.23 (−0.13, 0.59)	0.2085
TRANSPORT	0.17 (0.118)	0.61 (0.115)	0.44 (0.12, 0.77)	0.0078
Pooled	0.30 (0.088)	0.63 (0.087)	0.33 (0.08, 0.57)	0.0088
BMI (≥18 years)				
TRAFFIC	0.11 (0.081)	0.20 (0.083)	0.09 (−0.14, 0.32)	0.4344
TRANSPORT	0.03 (0.077)	0.35 (0.078)	0.33 (0.11, 0.54)	0.0027
Pooled	0.07 (0.056)	0.28 (0.057)	0.21 (0.05, 0.37)	0.0081



BMI = body mass index; CI = confidence interval; LSMD = least squares mean difference; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; MMRM = mixed-effects model for repeated measures; q12h = every 12 hours; SE = standard error.
Notes:

- MMRM model included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 versus ≥ 18 years), ppFEV$_1$ severity at screening (< 70% versus ≥ 70%), and the baseline value for the end point of interest.[12,13]
- Figure shows the difference in change from baseline in BMI for LUM/IVA versus placebo in TRAFFIC (●), TRANSPORT (▲), and a pooled analysis conducted by the manufacturer (■).

FIGURE 9: CHANGE FROM BASELINE IN Z SCORES FOR BODY MASS INDEX, BODY WEIGHT, AND HEIGHT



BMI = body mass index; CI = confidence interval; LSMD = least squares mean difference; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; MMRM = mixed-effects model for repeated measures; q12h = every 12 hours; SE = standard error.
Notes:

- MMRM model included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 versus ≥ 18 years), ppFEV$_1$ severity at screening (< 70% versus ≥ 70%), and the baseline value for the end point of interest.[12,13]
- Figure shows the difference in change from baseline in z scores for BMI, body weight, and height for LUM/IVA versus placebo in TRAFFIC (●), TRANSPORT (▲), and a pooled analysis conducted by the manufacturer (■).

3.6.4 Body Weight and Height

Changes in body weight and height were secondary end points in the included studies. It is important to note, however, that these outcomes were outside of the pre-specified statistical testing strategy, which means the analyses are considered to be exploratory, and the results should be interpreted with caution. Similarly, the statistical testing for the pooled analyses for change from baseline in weight and height (including the z score analysis) were conducted without adjustment for multiplicity and should be interpreted with caution.

Neither study demonstrated a statistically significant difference for LUM/IVA compared with placebo for changes in height (Table 13) or height z score (Figure 9) after 24 weeks of treatment. Similar to changes in BMI, results for change from baseline in body weight were inconsistent across the TRAFFIC and TRANSPORT studies. In TRANSPORT, treatment with LUM/IVA was associated with statistically significant improvements in body weight (0.95 kg; 95% CI, 0.43 to 1.46) and body weight z score ([redacted]). In contrast, LUM/IVA failed to demonstrate a statistically significant difference for these end points in TRAFFIC. The pooled analysis demonstrated a statistically significant difference in favour of LUM/IVA for change from baseline in body weight (0.62 kg; 95% CI, [redacted]) and body weight z score ([redacted]) (Table 14).

TABLE 13: ABSOLUTE CHANGES FROM BASELINE IN BODY MASS INDEX, WEIGHT, AND HEIGHT AT WEEK 24

End Point	Study	Parameter	Placebo	LUM/IVA	LUM/IVA vs. Placebo	
					LSMD (95% CI)[b]	*P* value
BMI (kg/m^2)	TRAFFIC	n	184	176	0.13 (−0.07 to 0.32)	0.1938
		Baseline	21.03 (2.956)	21.68 (3.169)		
		LS mean (SE)	0.19 (0.070)	0.32 (0.071)		
	TRANSPORT	n	183	180	0.36 (0.17 to 0.54)	0.0001
		Baseline	21.02 (2.887)	21.32 (2.894)		
		LS mean (SE)	0.07 (0.066)	0.43 (0.066)		
	Pooled	n	367	356	0.24 (0.11 to 0.37)	0.0004
		Baseline	21.02 (2.918)	21.50 (3.034)		
		LS mean (SE)	0.13 (0.048)	0.37 (0.048)		
Weight (kg)	TRAFFIC	n	184	176	0.30 (−0.26 to 0.86)	0.2992
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	0.93 (0.202)	1.23 (0.205)		
	TRANSPORT	n	187	187	0.95 (0.43 to 1.46)	0.0003
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	0.44 (0.187)	1.38 (0.187)		
	Pooled	n	371	369	0.62 [redacted]	0.0013
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	0.69 (0.138)	1.31 (0.139)		
Height[a] (cm)	TRAFFIC	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	TRANSPORT	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	Pooled	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		

CI = confidence interval; LS = least squares; LSMD = least squares mean difference; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; MMRM = mixed-effects model for repeated measures; n = number of patients with events; ppFEV$_1$ = per cent predicted forced expiratory volume in 1 second; q12h = every 12 hours; SE = standard error; vs. = versus.

[a] This end point was evaluated for patients younger than 20 years of age.

[b] MMRM model included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 versus ≥ 18 years), ppFEV$_1$ severity at screening (< 70% versus ≥ 70%), and the baseline value for the end point of interest.[12,13]

Source: Clinical Study Reports for TRAFFIC[12] and TRANSPORT[13] and Common Technical Document sections 5.3.5.3.[16]

TABLE 14: ABSOLUTE CHANGES FROM BASELINE IN Z SCORES FOR BODY MASS INDEX, WEIGHT, AND HEIGHT AT WEEK 24

End Point	Study	Parameter	Placebo	LUM/IVA	LUM/IVA vs. Placebo	
					LSMD (95% CI)[b]	*P* value
BMI z score[a]	TRAFFIC	n	69	58	0.0781 (−0.062 to 0.218)	0.2713
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	0.015 (0.049)	0.093 (0.054)		
	TRANSPORT	n	53	58	0.222 (0.096 to 0.347)	0.0006
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	−0.067 (0.047)	0.154 (0.045)		

End Point	Study	Parameter	Placebo	LUM/IVA	LUM/IVA vs. Placebo	
					LSMD (95% CI)[b]	*P* value
	Pooled	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
Weight z score[a]	TRAFFIC	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	TRANSPORT	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	Pooled	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
Height z score[a]	TRAFFIC	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	TRANSPORT	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	Pooled	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		

CI = confidence interval; LS = least squares; LSMD = least squares mean difference; LUM/IVA = LUM 400 mg q12h + IVA 250 mg q12h; MMRM = mixed-effects model for repeated measures; n = number of patients with events; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; q12h = every 12 hours; SE = standard error.

[a] These end points were evaluated for patients younger than 20 years of age.

[b] MMRM model included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 versus ≥ 18 years), $ppFEV_1$ severity at screening (< 70% versus ≥ 70%), and the baseline value for the end point of interest.[12,13]

Source: Clinical Study Reports for TRAFFIC[12] and TRANSPORT[13] and Common Technical Document sections 5.3.5.3.[16]

3.6.5 Health-Related Quality of Life

a) Cystic Fibrosis Questionnaire–Revised

Difference in change from baseline for the respiratory domain of the CFQ-R-respiratory domain was a key secondary end point of the included studies and, therefore, was included in the manufacturer's pre-specified statistical testing hierarchy. The statistical testing hierarchy was stopped prior to this outcome in TRAFFIC; therefore, the results should be considered exploratory. Similarly, the statistical testing for the pooled analysis was conducted without adjustment for multiplicity and should be interpreted with caution.

There was no statistically significant difference between LUM/IVA and placebo for change from baseline to week 24 in the CFQ-R–respiratory domain (Table 15) in either individual studies or the pooled analysis (*P* = 0.0512). Based on the hierarchical testing procedure, the testing hierarchy stopped at this end point in the TRANSPORT study.

b) EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire–3 Levels

Changes in EQ-5D-3L utility scores and EQ-5D VAS were secondary end points in the included studies. It is important to note, however, that these outcomes were outside of the pre-specified statistical testing

strategy, which means the analyses are considered to be exploratory, and the results should be interpreted with caution.

There was no statistically significant difference between LUM/IVA and placebo for change from baseline to week 24 in the EQ-5D-3L utility scores or EQ-5D VAS (Table 15). For the EQ-5D-3L VAS, there was a numerical difference favouring LUM/IVA compared with placebo in TRANSPORT (mean difference 3.3; 95% CI, 0.4 to 6.2); however, the difference was not statistically significant (i.e., *P* = 0.0262). Pooled results for the EQ-5D index and VAS were not reported by the manufacturer for LUM/IVA versus placebo at 24 weeks.[16]

TABLE 15: ABSOLUTE CHANGE FROM BASELINE IN CFQ-R–RESPIRATORY DOMAIN AND EQ-5D-3L

End Point	Study		LS Mean Change (SE)		LUM/IVA Versus Placebo	
			Placebo	LUM/IVA	LSMD (95% CI)[a]	*P* value
CFQ-R (Respiratory domain)	TRAFFIC	n	184	181	1.50 (−1.69 to 4.69)	0.3569
		Baseline	70.54 (16.032)	69.29 (17.424)		
		LSM (SE)	1.10 (1.161)	2.60 (1.192)		
	TRANSPORT	n	185	179	2.85 (−0.27 to 5.98)	0.0736
		Baseline	67.05 (18.394)	67.36 (18.540)		
		LSM (SE)	2.81 (1.153)	5.66 (1.169)		
	Pooled	n	369	351	2.22 (−0.01 to 4.45)	0.0512
		Baseline	68.78 (17.328)	68.31 (17.998)		
		LSM (SE)	1.88 (0.818)	4.10 (0.834)		
EQ-5D-3L (utility score)	TRAFFIC	n	179	170	0.0095 (−0.0109 to 0.0298)	0.3613
		Baseline	0.9237 (0.10371)	0.9217 (0.09774)		
		LSM (SE)	0.0006 (0.0074)	0.01 (0.0076)		
	TRANSPORT	n	183	176	−0.0009 (−0.0192 to 0.0174)	0.9214
		Baseline	0.9171 (0.10837)	0.9267 (0.10462)		
		LSM (SE)	0.0117 (0.00673)	0.0108 (0.00683)		
EQ-5D-3L (VAS)	TRAFFIC	n	180	171	1.4 (−1.3 to 4.2)	0.3071
		Baseline	[redacted]	[redacted]		
		LSM (SE)	1.4 (1.03)	2.8 (1.04)		
	TRANSPORT	n	182	177	3.3 (0.4 to 6.2)	0.0262
		Baseline	72.8 (17.36)	71.8 (21.76)		
		LSM (SE)	3.3 (1.07)	6.6 (1.08)		

CFQ-R = Cystic Fibrosis Questionnaire–Revised; CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire–3 Levels; LS = least squares; LSMD = least squares mean difference; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; MMRM = mixed-effects model for repeated measures; n = number of patients with events; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; q12h = every 12 hours; SE = standard error; VAS = visual analogue score.

[a] MMRM model included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 versus ≥ 18 years), $ppFEV_1$ severity at screening (< 70% versus ≥ 70%), and the baseline value for the end point of interest.[12,13]

Source: Clinical Study Reports for TRAFFIC[12] and TRANSPORT[13] and Common Technical Document section 5.3.5.3.[16]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See APPENDIX 4: DETAILED OUTCOME DATA for detailed harms data. In accordance with the manufacturer's safety analysis plan,[15] this section of the report summarizes pooled adverse events from TRAFFIC and TRANSPORT. The pooled data set consists of the following:

- 369 patients who received LUM 400 mg every 12 hours/IVA 250 mg every 12 hours
- 369 patients who received LUM 600 mg once daily/IVA 250 mg every 12 hours
- 370 patients who received placebo.

As noted earlier, the CDR systematic review is focused only on the Health Canada–approved dosage of LUM/IVA; therefore, data for the LUM 600 mg once daily/IVA 250 mg every 12 hours dosage regimen are not summarized.

A summary of adverse events from the pooled TRAFFIC and TRANSPORT studies is provided in Table 16. The overall proportion of patients who experienced at least one adverse event was similar between the placebo group (95.9%) and the LUM/IVA group (95.1%). The proportion of patients who experienced at least one SAE was lower in the LUM/IVA group compared with the placebo group (28.6% versus 17.3%, respectively); however, WDAEs were more frequent in the LUM/IVA group compared with the placebo group (4.6% versus 1.6%, respectively). There were no deaths in TRAFFIC and TRANSPORT.[15]

TABLE 16: SUMMARY OF ADVERSE EVENTS IN TRAFFIC AND TRANSPORT

Adverse Events, n (%)	TRAFFIC and TRANSPORT	
	Placebo N = 370	LUM/IVA N = 369
Any adverse events	355 (95.9)	351 (95.1)
Adverse events leading to discontinuation	6 (1.6)	17 (4.6)
Adverse events leading to interruption	25 (6.8)	22 (6.0)
Grade 3 or 4 adverse events	59 (15.9)	45 (12.2)
Serious adverse events	106 (28.6)	64 (17.3)
Adverse events leading to death	0	0

LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients with events; q12h = every 12 hours.
Sources: Reproduced from Common Technical Document section 2.7.4[15]

3.7.1 Adverse Events

The overall proportion of patients who experienced at least one adverse event was similar between the placebo groups (95.9%) and the LUM/IVA groups (95.1%). The most commonly reported adverse events in both the placebo and LUM/IVA groups (respectively) were infective pulmonary exacerbations (49.2% versus 35.8%), cough (40.0% versus 28.2%), headache (15.7% versus 15.7%), and increases in sputum (18.9% versus 14.6%). Adverse events that were reported in ≥ 5% of patients in the LUM/IVA group and occurred at higher frequency compared with the placebo group were dyspnea (13% versus 8%); abnormal respiration (9% versus 6%); rhinorrhea (6% versus 4%); nasopharyngitis (13% versus 11%); upper respiratory tract infection (10% versus 5%); influenza (5% versus 2%); nausea (13% versus 8%); diarrhea (12% versus 8%); flatulence (7% versus 3%); fatigue (9% versus 8%); increased blood creatine phosphokinase (7% versus 5%), and rash (7% versus 2%).[15]

Consistent with the efficacy data, there were fewer pulmonary exacerbations in the placebo group compared with the LUM/IVA. In addition, fewer LUM/IVA-treated patients reported cough, sputum

increase, nasal congestion, or experienced a decreased pulmonary function test with LUM/IVA compared with placebo.[15]

TABLE 17: MOST COMMON ADVERSE EVENTS (≥ 5% PATIENTS) IN TRAFFIC AND TRANSPORT

AEs, n (%)	TRAFFIC and TRANSPORT	
	Placebo N = 370	LUM/IVA N = 369
Any AEs	355 (95.9)	351 (95.1)
Infective pulmonary exacerbation of CF	182 (49.2)	132 (35.8)
Cough	148 (40.0)	104 (28.2)
Headache	58 (15.7)	58 (15.7)
Sputum, increased	70 (18.9)	54 (14.6)
Dyspnea	29 (7.8)	48 (13.0)
Hemoptysis	50 (13.5)	50 (13.6)
Diarrhea	31 (8.4)	45 (12.2)
Nausea	28 (7.6)	46 (12.5)
Respiration, abnormal	22 (5.9)	32 (8.7)
Nasopharyngitis	40 (10.8)	48 (13.0)
Oropharyngeal pain	30 (8.1)	24 (6.5)
Pyrexia	34 (9.2)	33 (8.9)
Fatigue	29 (7.8)	34 (9.2)
Upper respiratory tract infection	20 (5.4)	37 (10.0)
Abdominal pain	32 (8.6)	33 (8.9)
Nasal congestion	44 (11.9)	24 (6.5)
Viral upper respiratory tract infection	25 (6.8)	23 (6.2)
Rhinitis	18 (4.9)	16 (4.3)
Flatulence	11 (3.0)	24 (6.5)
Blood creatine phosphokinase, increased	20 (5.4)	27 (7.3)
Rash	7 (1.9)	25 (6.8)
Sinusitis	19 (5.1)	16 (4.3)
Rhinorrhea	15 (4.1)	21 (5.7)
Vomiting	11 (3.0)	16 (4.3)
Influenza	8 (2.2)	19 (5.1)
Abdominal pain, upper	18 (4.9)	12 (3.3)
Constipation	21 (5.7)	14 (3.8)
Pulmonary function test, decreased	20 (5.4)	3 (0.8)

AE = adverse event; CF = cystic fibrosis; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients with events; q12h = every 12 hours.
Sources: Reproduced from Common Technical Document section 2.7.4.[15]

3.7.2 Serious Adverse Events

Table 18 provides a summary of SAEs in the pooled TRAFFIC and TRANSPORT studies. The proportion of patients who experienced at least one SAE was greater in the placebo group (28.6%) than in the LUM/IVA group (17.3%). The most commonly reported SAE in any treatment group was infective pulmonary exacerbation of CF. Consistent with the efficacy data reported in section 0, there were more pulmonary exacerbations in the placebo group than in the LUM/IVA group (24.1% versus 11.1%, respectively).

TABLE 18: SERIOUS ADVERSE EVENTS

SAEs, n (%)	TRAFFIC and TRANSPORT	
	Placebo N = 370	LUM/IVA N = 369
Any SAEs	106 (28.6)	64 (17.3)
Infective pulmonary exacerbation of CF	89 (24.1)	41 (11.1)
Pneumonia	0	1 (0.3)
Influenza	2 (0.5)	0
Bronchitis	2 (0.5)	0
Hemoptysis	3 (0.8)	5 (1.4)
Cough	0	1 (0.3)
Distal intestinal obstruction syndrome	5 (1.4)	2 (0.5)
Constipation	2 (0.5)	1 (0.3)
Blood creatine phosphokinase, increased	0	2 (0.5)
Nephrolithiasis	2 (0.5)	1 (0.3)
Deep vein thrombosis	2 (0.5)	0

CF = cystic fibrosis; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients with events; q12h = every 12 hours; SAE = serious adverse event.
Source: Adapted from Common Technical Document section 2.7.4.[15]

3.7.3 Withdrawals Due to Adverse Events

WDAEs were more common in the LUM/IVA group compared with the placebo (4.6% versus 1.6%). An increase in blood creatine phosphokinase resulted in the discontinuation of four LUM/IVA patients compared with none in the placebo groups. Hemoptysis was the most commonly reported adverse event that resulted in patients discontinuing treatment (two patients in the placebo group and three patients in the LUM/IVA group). The only other adverse events that resulted in discontinuation of more than one patient were bronchospasm, dyspnea, pulmonary exacerbation, and rash.[15]

TABLE 19: WITHDRAWALS DUE TO ADVERSE EVENTS

WDAEs, n (%)	TRAFFIC and TRANSPORT	
	Placebo N = 370	LUM/IVA N = 369
Any WDAEs	6 (1.6)	17 (4.6)
Hemoptysis	2 (0.5)	3 (0.8)
Blood creatine phosphokinase, increased	0	4 (1.1)
Forced expiratory volume, decreased	0	1 (0.3)
Pulmonary function test, decreased	0	1 (0.3)
Blood alkaline phosphatase, increased	1 (0.3)	0
Nausea	0	1 (0.3)
Infective pulmonary exacerbation of CF	0	2 (0.5)
Hepatic encephalopathy	0	1 (0.3)
Rash	0	1 (0.3)
Acne	1 (0.3)	0
Thrombocytosis	0	1 (0.3)
Drug hypersensitivity	0	1 (0.3)

WDAEs, n (%)	TRAFFIC and TRANSPORT	
	Placebo N = 370	LUM/IVA N = 369
Myalgia	0	1 (0.3)
Renal cancer	1 (0.3)	0
Bradyphrenia	1 (0.3)	0

CF = cystic fibrosis; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients with events; q12h = every 12 hours; WDAE = withdrawal due to adverse event.
Source: Adapted from Common Technical Document section 2.7.4.[15]

3.7.4 Notable Harms

The manufacturer identified respiratory symptoms, reactive airways, and elevated transaminases as adverse events of special interest in its analysis of safety data from TRAFFIC and TRANSPORT.[15] In consultation with the clinical expert, the CDR review included the respiratory adverse events as well as hepatic adverse events as additional harms of interest.

a) Hepatic adverse events

Hepatic adverse events in TRAFFIC and TRANSPORT are summarized in Table 20. The proportion of patients who experienced at least one hepatic adverse event was similar in the LUM/IVA group (6.0%) and the placebo group (5.4%). Elevated transaminases were reported in a slightly greater proportion of LUM/IVA-treated patients compared with placebo-treated patients (5.4% versus 4.6%); however, this represented a difference of only three patients. Serious liver-related AEs were reported for three patients in the LUM/IVA group and none in the placebo group.

TABLE 20: HEPATIC ADVERSE EVENTS

Hepatic AEs, n (%)	TRAFFIC and TRANSPORT	
	Placebo N = 370	LUM/IVA N = 369
Any liver-related AEs	20 (5.4)	22 (6.0)
Elevated transaminases	17 (4.6)	20 (5.4)
Alanine aminotransferase, increased	9 (2.4)	8 (2.2)
Aspartate aminotransferase, increased	8 (2.2)	9 (2.4)
Hepatic enzyme, increased	0	4 (1.1)
Liver function test, abnormal	6 (1.6)	3 (0.8)
Transaminases, increased	1 (0.3)	2 (0.5)
Any other hepatobiliary disorder AEs	3 (0.8)	3 (0.8)
Biliary colic	0	1 (0.3)
Hepatic pain	0	1 (0.3)
Hepatitis	1 (0.3)	0
Cholecystitis acute	1 (0.3)	0
Cholelithiasis	1 (0.3)	0
Hepatic encephalopathy	0	1 (0.3)
Liver-related AEs leading to discontinuation	0	1 (0.3)
Liver-related AEs leading to interruption	4 (1.1)	4 (1.1)
Serious liver-related AEs	0	3 (0.8)

AE = adverse event; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients with events; q12h = every 12 hours.
Source: Adapted from Common Technical Document section 2.7.4.[15]

b) Respiratory adverse events

TRAFFIC and TRANSPORT included two categories of respiratory adverse events of special interest: respiratory symptoms and reactive airways. These categories were established based on observations from the phase 2 clinical trials, in which treatment with LUM appeared to be associated with an increased risk of respiratory adverse events during the treatment-initiation period. As shown in Table 21, a greater proportion of LUM/IVA-treated patients (25.7%) had at least one respiratory adverse event compared with those who were treated with placebo (17.0%). This difference was primarily attributable to the greater proportion of LUM/IVA-treated patients (22.0%) who experienced adverse events related to respiratory symptoms compared with placebo (13.8%). The proportion of patients with reactive airway adverse events was similar in the LUM/IVA group (6.5%) compared with the placebo group (5.4%), with a difference of only four patients.[15] Nearly all respiratory adverse events were mild or moderate in severity.[1]

Of the 81 LUM/IVA-treated patients who experienced at least one adverse event related to respiratory symptoms, 80.2% (n = 65) experienced the event during the first week of treatment (Table 22). The occurrence of events was sharply reduced after the first week and the manufacturer reported that there was no difference between the LUM/IVA and placebo groups after the first week. The median time to onset of respiratory symptom adverse events was two days in the LUM/IVA group and 43 days in placebo group. The mean duration of the respiratory adverse events was 18.5 days in the LUM/IVA group and 12.9 days in the placebo group.

The manufacturer conducted subgroup analyses to explore the occurrence of the respiratory adverse events based on $ppFEV_1$ at screening (< 70% or ≥ 70%) and at baseline (< 40% or ≥ 40%). As shown in Table 28, in both analyses, dyspnea was more commonly reported for patients with poorer lung function. In the LUM/IVA groups, there was approximately a two-fold increase in dyspnea in the following: patients with $ppFEV_1$ < 70% compared with ≥ 70% (16.3% versus 7.0), and patients with $ppFEV_1$ < 40% compared with ≥ 40% (24.1% versus 12.2). Dyspnea was also more commonly reported in placebo-treated patients who had a poorer lung function.

TABLE 21: RESPIRATORY ADVERSE EVENTS

Respiratory AEs, n (%)	TRAFFIC and TRANSPORT	
	Placebo N = 370	LUM/IVA N = 369
Respiratory symptoms		
Any AESI of respiratory symptoms	51 (13.8)	81 (22.0)
Chest discomfort	5 (1.4)	7 (1.9)
Dyspnea	29 (7.8)	48 (13.0)
Respiration, abnormal	22 (5.9)	32 (8.7)
Leading to discontinuation	0	0
Leading to interruption	1 (0.3)	0
Mild	37 (10.0)	61 (16.5)
Moderate	12 (3.2)	20 (5.4)
Severe	2 (0.5)	0
Life-threatening	0	0
Reactive airways		
Any AE of reactive airways	20 (5.4)	24 (6.5)

Respiratory AEs, n (%)	TRAFFIC and TRANSPORT	
	Placebo N = 370	LUM/IVA N = 369
Asthma	5 (1.4)	8 (2.2)
Bronchial hyperreactivity	0	2 (0.5)
Bronchospasm	1 (0.3)	5 (1.4)
Wheezing	15 (4.1)	11 (3.0)
Leading to discontinuation	0	0
Leading to interruption	0	0
Mild	16 (4.3)	16 (4.3)
Moderate	4 (1.1)	8 (2.2)
Severe	0	0
Life-threatening	0	0

AE = adverse event; AESI = adverse event of special interest; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients with events; q12h = every 12 hours.
Source: Adapted from Common Technical Document section 2.7.4.[15]

TABLE 22: TIMING OF ONSET AND DURATION OF RESPIRATORY ADVERSE EVENTS

Adverse Events, n (%)	Pooled TRAFFIC and TRANSPORT			
	Respiratory symptoms		Reactive airways	
	Placebo N = 370	LUM/IVA N = 369	Placebo N = 370	LUM/IVA N = 369
Any events, n (%)	51 (13.8)	81 (22.0)	20 (5.4)	24 (6.5)
> 0 to ≤ 1 week	14 (3.8)	65 (17.6)	6 (1.6)	8 (2.2)
> 1 to ≤ 2 weeks	4 (1.1)	4 (1.1)	2 (0.5)	3 (0.8)
> 2 to ≤ 8 weeks	17 (4.6)	10 (2.7)	8 (2.2)	6 (1.6)
> 8 to ≤ 16 weeks	14 (3.8)	8 (2.2)	4 (1.1)	8 (2.2)
> 16 to ≤ 24 weeks	9 (2.4)	8 (2.2)	2 (0.5)	3 (0.8)
> 24 weeks	1 (0.3)	1 (0.3)	0	0
Time to onset, days				
Mean (SD)	51.7 (51.53)	18.9 (41.52)	34.3 (33.28)	48.3 (46.77)
Median	43.0	2.0	22.0	50.0
Duration of events, days				
Number of events	65	102	23	30
Mean (SD)	12.9 (15.01)	18.5 (26.52)	14.6 (15.00)	20.6 (39.97)
Median	6.5	6.0	10.0	6.0

LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients with events; q12h = every 12 hours; SD = standard deviation.
Source: Common Technical Document section 2.7.4.[15]

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was derived primarily from two identically-designed, phase 3, randomized, double-blind, placebo-controlled trials (TRAFFIC and TRANSPORT) conducted to evaluate the efficacy and safety of LUM/IVA in patients aged 12 years and older with CF who were homozygous for the F508del-CFTR mutation. The CDR review focused on the use of LUM/IVA at the Health Canada–approved dosage (i.e., LUM 400 mg every 12 hours/IVA 250 mg every 12 hours). Both TRAFFIC and TRANSPORT also included an additional LUM/IVA dosage regimen (LUM 600 mg once daily/IVA 250 mg every 12 hours), which was excluded from the CDR review as this dosage regimen is not currently approved by Health Canada and could not be administered using the formulation of LUM/IVA that is marketed in Canada (i.e., tablets containing 200 mg of lumacaftor and 125 mg of ivacaftor). The data from the two pivotal RCTs are limited to 24 weeks of double-blind treatment; therefore, the CDR review also considered supplemental 48-week data from a longer-term extension study (PROGRESS). These data were accumulated from 24 weeks of exposure in the pivotal trials and 24 weeks of exposure in the extension study.

The TRAFFIC and TRANSPORT studies were generally well conducted. Both studies evaluated a range of different outcomes that are considered to be important in the management of CF, including respiratory function (i.e., ppFEV$_1$), nutritional status and growth (e.g., weight, height, and BMI), health-related quality of life (i.e., CFQ-R and EQ-5D-3L), and clinical events (e.g., pulmonary exacerbations). The manufacturer reported that the trials did not include changes in sweat chloride, a commonly used biochemical marker in CF trials, as the effect of LUM/IVA on sweat chloride was established in the phase 2 studies of the clinical development program.[31]

The Health Canada–approved indication for LUM/IVA reflects the age of the patients who were enrolled in the pivotal studies (i.e., patients who are at least 12 years of age). Given that CF-related damage to organ systems can be irreversible,[39] it is likely that patients in Canada who could be eligible for treatment with LUM/IVA would initiate treatment as soon as possible. The manufacturer indicated that the age range for the TRAFFIC and TRANSPORT studies was selected because compared with adult patients, those aged 12 years and older can be enrolled using common eligibility criteria, administered the same dosages of study drugs, and evaluated using the same end points. It was noted that studies in younger patients require a modified study protocol to determine safe and efficacious dosage regimens in that population.[31] As such, the manufacturer is currently completing phase 3, open-label studies (VX13-809-011 [N = 58] and VX14-809-109 [N = 200]) evaluating the pharmacokinetics and tolerability of LUM/IVA in patients aged six to 11 years with CF who are homozygous for the F508del-CFTR mutation.[51,52] These studies are investigating a lower dosage of LUM (i.e., 200 mg of every 12 hours) compared to the 400 mg every 12 hours that is currently recommended in patients 12 years and older.[51,52]

TRAFFIC and TRANSPORT excluded patients who were infected with some *B. cepacia* complex species (i.e., *B. cenocepacia* and *B. dolosa*). These patients represent approximately 5% of the CF patient population in Canada; however, the clinical expert consulted by CDR noted that the exclusion of such patients does not substantially reduce the generalizability of the study results. This is similar to the opinion of the Cystic Fibrosis Foundation in the US, in its publication on the considerations for the use of LUM/IVA, in which it suggested that there is no basis to conclude that CF patients with these infections would not benefit from treatment with LUM/IVA. Furthermore, the Cystic Fibrosis Foundation noted

that such patients may derive the greatest benefit from treatment with LUM/IVA, as they are at increased risk for accelerated disease progression and mortality.[39] The manufacturer has stated that it is conducting post-market studies to collect data on the use of LUM/IVA in patients infected with *B. cepacia* complex species (details were not provided); however, until these data are available, this remains a relevant research gap.

4.2 Interpretation of Results

4.2.1 Efficacy

After 24 weeks of treatment, LUM/IVA was associated with a statistically significant improvement in $ppFEV_1$ compared with placebo (absolute improvement of 2.6% to 3.0%). The treatment effect observed in the pivotal trials was lower than the 5% difference that was assumed by the manufacturer when conducting the sample size calculations for the studies.[5] The clinical expert consulted for this review indicated that a change in $ppFEV_1$ of the magnitude observed in the TRAFFIC and TRANSPORT studies was modest and of uncertain clinical benefit. While CDR identified no published information on the MCID in absolute change in $ppFEV_1$ in CF, the clinical expert consulted by CDR noted that CF specialists would generally consider an absolute improvement in $ppFEV_1$ of ≥ 5% to be clinically significant. The clinical expert consulted by NICE in the UK also cited an absolute change of at least 5% as the MCID by.[49] The committee for NICE concluded that the improvements in $ppFEV_1$ observed with LUM/IVA in the pivotal studies were unlikely to be clinically significant.[8]

Although the magnitude of improvement is small, reviewers for Health Canada, the EMA, and the FDA concluded that, because FEV_1 is correlated with mortality, the observed improvement in FEV_1 may be clinically relevant for patients with F508del mutations.[5-7] Given the correlation between lung function and mortality in CF, Health Canada concluded that any of the following could be considered clinically relevant for CF patients: stabilization of lung function, an improvement in the rate of decline of lung function, or a marginal improvement in lung function.[7]

The magnitude of the treatment effect reported in the TRAFFIC and TRANSPORT studies is considerably lower than the 10.6% to 12.5% improvement in $ppFEV_1$ at 24 weeks that was observed with ivacaftor monotherapy in the treatment of patients with CF with gating mutations (STRIVE, ENVISION, and KONNECTION).[44-46] It is also lower than the 5.0% improvement in $ppFEV_1$ that was observed with ivacaftor in adults with the R117H mutation (KONDUCT).[47] Reviewers for the EMA suggested that the reduced efficacy in the TRAFFIC and TRANSPORT studies compared with those conducted in patients with gating mutations is due to the more severe defects of the CFTR protein that are caused by the F508del mutation.[5]

Fewer than half of LUM/IVA-treated patients in TRAFFIC and TRANSPORT demonstrated an improvement of ≥ 3% in $ppFEV_1$ and fewer than one-third achieved an absolute increase of ≥ 5% in $ppFEV_1$. Given the large proportion of patients who failed to achieve an improvement of at least 5% in $ppFEV_1$ and the rapid onset of treatment effects (i.e., within two weeks of initiating therapy), the EMA asked the manufacturer to consider developing the following: criteria that could be used to identify non-responders shortly after the initiation or treatment; and stopping criteria to avoid unnecessary exposure of patients who are unlikely to benefit clinically from treatment with LUM/IVA.[5] However, because LUM/IVA demonstrated a reduction in pulmonary exacerbations regardless of whether there was an improvement in $ppFEV_1$ after two weeks of treatment, the manufacturer and the EMA agreed that the identification of non-responders should not be based on early $ppFEV_1$ response.[5]

The ability of a treatment such as LUM/IVA to result in longitudinal changes in $ppFEV_1$ is more clinically relevant than acute changes in $ppFEV_1$.[8] However, TRAFFIC and TRANSPORT were too short for conclusions to be drawn regarding whether or not treatment with LUM/IVA would reduce the slope of decline in $ppFEV_1$. Given that LUM/IVA would likely be used as a long-term treatment for CF, a chronic condition, the absence of long-term efficacy data is an important research gap. Twenty-four-week data from the first interim analysis of the PROGRESS extension study suggested that patients treated with LUM/IVA maintained the effects that were observed in the double-blind phase of TRAFFIC and TRANSPORT (absolute improvement of 2.5% from baseline; $P < 0.0001$). Data from the Canadian Cystic Fibrosis Registry (2013) suggest that CF patients undergo a decline in lung function of 0.2% per year between the ages of six and 11 years. For patients who would be eligible for treatment with LUM/IVA (i.e., those aged 12 years and older), the registry data suggest that there is an average decline of 2.6% per year between the ages of 11 and 23 years, before stabilizing to an average decrease of 0.7% per year after age 23.[3]

Pulmonary exacerbations are currently the most common reason for hospitalization of CF patients[3] and, accordingly, these events were identified as an outcome of interest by Cystic Fibrosis Canada in its input for this review (Appendix 1). Pulmonary exacerbations are clinically significant events for patients with CF and are correlated with increased mortality, greater decline in lung function, reduced quality of life, and increased health costs.[53-57] In addition, it has been estimated that many CF patients experience a permanent reduction in lung function following an exacerbation (i.e., their lung function will not recovery to the level it was prior to the exacerbation). In a large sample of CF patients (N = 8,479), Sanders et al. (2010) estimated that 25% of CF patients who experienced a pulmonary exacerbation failed to recover to their baseline FEV_1.[58] A similar observation has been made in an analysis in pediatric CF patients, in which 23% of patients failed to recover to their baseline FEV_1 after being treated with IV antibiotics for a pulmonary exacerbation.[59]

Treatment with LUM/IVA was associated with a likely clinically meaningful reduction in the risk of pulmonary exacerbations, including those requiring hospitalization and IV antibiotic therapy. The statistical hierarchy was stopped prior to testing for statistical significance of the observed reduction in pulmonary exacerbations; however, the occurrence of exacerbations was lower in the LUM/IVA group of both pivotal studies compared with placebo. There appears to be consensus from regulatory authorities (e.g., EMA and FDA), health technology assessment agencies (e.g., NICE), and the clinical expert consulted by CDR that the observed reduction in pulmonary exacerbations with LUM/IVA is likely to be clinically meaningful; however, claims of statistical significance cannot be made.[5,8]

The treatment effect with LUM/IVA was relatively consistent across all of the subgroups that were studied in TRAFFIC and TRANSPORT; however, due to the small number of patients, the results for some subgroup analyses (e.g., $ppFEV_1 < 40\%$ or age 12 to 18 years) are limited by imprecise estimates of effect (e.g., wide confidence intervals) and inconsistency across studies (e.g., significance demonstrated in only one of the two trials). Patients with a $ppFEV_1$ below 40% at screening were excluded from the trial; however, a number of patients (n = 81) satisfied the screening requirements, but had $ppFEV_1$ below 40% at baseline (i.e., their $ppFEV_1$ was above 40% in the screening phase, then fell below 40% at their baseline evaluation). Reviewers for the EMA noted that patients with baseline $ppFEV_1 < 40\%$ had absolute improvements in $ppFEV_1$ that were comparable to those reported for patients with $ppFEV_1$ of at least 40%.[5] Consistent with the improvements in $ppFEV_1$, there was a numerical reduction in the pulmonary exacerbation event rate observed in the TRANSPORT study in patients with $ppFEV_1$ less than 40 (19 versus 10 events per year).

Given that LUM/IVA is a systemic treatment, the TRAFFIC and TRANSPORT studies included end points such as BMI, body weight, and height to evaluate the effect of treatment on the nutritional status of CF patients. Results for change from baseline in BMI and weight were inconsistent across the pivotal studies, with statistically significant improvements observed in TRANSPORT but not in TRAFFIC. However, a meta-analysis of these studies demonstrated that treatment with LUM/IVA was associated with improvements in BMI and BMI z scores. Overall, the pooled data from the pivotal studies and the interim analysis from the PROGRESS extension study suggest that BMI and body weight gradually improved for patients treated with LUM/IVA (e.g., [redacted]). Given the relatively short-term data available, the clinical relevance of the observed changes in BMI is uncertain; however, reviewers for the FDA commented that LUM/IVA failed to demonstrate consistent clinical benefit in BMI.[41]

As stated in the patient group input, CF has a major impact on the quality of life of patients and their caregivers. Treatment with LUM/IVA did not demonstrate statistically significant improvements in health-related quality of life (i.e., CFQ-R or EQ-5D-3L) in either TRAFFIC or TRANSPORT. The manufacturer has reported that this could be due to a ceiling effect. This may at least be true for the EQ-5D utility score: given that mean baseline score was [redacted], there would be little room for patients to improve in both trials. However, the EQ-5D has not been formally evaluated as a measure of health-related quality of life in CF.[8] This perspective was shared by patient experts who provided input on NICE's review of LUM/IVA.[8] It must be noted that the use of ivacaftor monotherapy in patients with CF-gating mutations was associated with greater improvements in the CFQ-R (i.e., 6.1% to 8.1%)[44,45] than was observed with LUM/IVA in TRAFFIC and TRANSPORT. In addition, treatment with ivacaftor resulted in a statistically significant improvement in EQ-5D compared with placebo, although the magnitude of improvement was not considered to be clinically relevant.

LUM/IVA was studied as an add-on treatment to a stable regimen of CF therapy. There is no evidence to suggest that LUM/IVA may replace or minimize the need for current treatments that are used on a daily basis. However, treatment with LUM/IVA was associated with a reduction in the need for IV antibiotics and hospitalization, important outcomes that could reduce the overall treatment burden for CF patients and their caregivers.[5]

4.2.2 Harms

LUM/IVA appears to be generally well tolerated in the target patient population, as represented in the TRAFFIC and TRANSPORT studies.[2] The most common adverse events associated with LUM/IVA were respiratory and gastrointestinal. WDAEs were more common in the LUM/IVA group compared with the placebo group in both pivotal studies; however, more than 95% of LUM/IVA-treated patients completed the 24-week treatment period. The clinical expert consulted by CDR noted that patients who experience significant adverse events following initial treatment with LUM/IVA would not likely be completely discontinued from treatment; rather, treatment with LUM/IVA would probably be interrupted and the patient would be re-challenged with the drug following resolution of the event(s).

The product monograph notes the potential for serious respiratory, hepatic, and cardiovascular adverse events in patients receiving LUM/IVA and it is recommended that patients be monitored, particularly during the phase when treatment is being initiated.[1] The clinical expert consulted by CDR noted that the monitoring requirements associated with LUM/IVA could result in an additional two visits during the first year of treatment. Experts consulted by NICE also noted that patients undergoing treatment with LUM/IVA would require additional counselling and monitoring.[49]

The product monograph recommends that the dosage of LUM/IVA should be adjusted in patients with mild, moderate, or severe hepatic impairment. The clinical expert consulted by CDR noted that the vast majority of patients who could be eligible for LUM/IVA would not have hepatic impairment. There have been no studies conducted in patients with severe hepatic impairment, and the product monograph recommends that treatment with LUM/IVA should be used with caution in such patients and only after weighing the risks and benefits of treatment. Similar to the pivotal studies from the ivacaftor development program,[44,45,47] patients with abnormal liver function were excluded from the TRAFFIC and TRANSPORT studies.[31]

LUM/IVA was associated with an increase in the occurrence of respiratory adverse events (e.g., dyspnea and abnormal respiration) compared with placebo. Nearly all of these events were mild to moderate in severity, occurred shortly after the initiation of treatment, and typically resolved within a few weeks of treatment. The respiratory adverse events occurred more frequently in patients with poorer lung function; however, the severity of these events was generally similar, regardless of baseline lung function.[9] The Canadian product monograph currently contains a warning regarding the observed increase in respiratory adverse events with LUM/IVA, and also notes that clinical experience with LUM/IVA in patients with $ppFEV_1 < 40\%$ is limited, and that additional monitoring of these patients is recommended during the initiation of therapy.[1] The clinical expert consulted by CDR noted that the issue of respiratory adverse events is an area of concern in the clinical community, particularly with respect to patients who have poor lung function. There are currently no guidelines that specifically address the management of these events in clinical practice.

4.3 Other Considerations

NICE in the UK recently issued a draft recommendation (pending final determination in July 2016) stating it does not recommend that LUM/IVA be funded for treating CF in people of 12 years and older who are homozygous for the F508del mutation in the CFTR gene.[8] NICE's Technology Appraisal Committee (TAC) noted that the improvements in $ppFEV_1$ observed in the TRAFFIC and TRANSPORT studies were unlikely to be clinically significant, but that the reductions in pulmonary exacerbations were clinically significant. Overall, the TAC concluded that the estimated incremental cost-effective ratios for LUM/IVA exceed the levels that are typically considered to represent a cost-effective use of health care resources. Similarly, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia issued a decision stating that LUM/IVA was not recommended for listing on the Pharmaceutical Benefits Scheme. The committee cited unacceptably high and uncertain incremental cost-effectiveness and uncertainty regarding the impact of LUM/IVA on long-term improvements in lung function and survival for CF patients.[10] The Scottish Medicines Consortium (SMC) also concluded that LUM/IVA was not recommended for use within NHS Scotland. The SMC noted that the cost of LUM/IVA relative to the health benefits it offered was insufficient.[11]

4.4 Potential Place in Therapy

This information in this section is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

The clinical expert involved in the review noted that despite several advances in drug therapies and resulting improved outcomes in the management of CF, there remains an unmet need for better CF therapies. The mechanism of action of LUM/IVA is completely different from current standard of care. Uncertain clinically significant improvement in FEV_1, but a likely clinically significant reduction in pulmonary exacerbations, was seen with LUM/IVA when given in addition to standard CF therapy in phase 3 trials (i.e., TRANSPORT and TRAFFIC). Although short-term change in FEV_1 was the primary

outcome of the studies, this is probably not the most important measure, as it is the rate of decline in lung function and number of exacerbations that is associated with progression of disease and survival.[55] It is not generally feasible to conduct trials to look at change in rate of FEV_1, as decline in FEV_1 is now only 1% to 2.5% per year.[26,55,60] Reduction in exacerbations is likely the best surrogate marker available. Long-term therapy with other CF drugs such as dornase alpha and inhaled antibiotics has been shown to be associated with significant reduction in lung function decline[61] and improvement in survival.[62] Thus, the magnitude of change in number of exacerbations seen with LUM/IVA in the phase 3 trials may be clinically significant.

Patients who will receive this medication will all be followed in CF clinics by specialized physicians. The F508del mutation is identified in the standard genetic screening panel and in the newborn screening panel, and 96% of CF patients have had genotyping done.[3] In adult patients, the clinical expert consulted for the review suggested that the patients started on therapy will be those with evidence of lung disease, who are on standard of care and who are showing deterioration in lung function. Given a degree of uncertainty with respect to the results of the two trials, the clinical expert stated that stable adults with good lung function may not perceive significant benefits to a trial of therapy with LUM/IVA. Additionally, the clinical expert indicated that parents of children with CF may want their children to be started on therapy, even if they have minimal lung function impairment. Patients enrolled in CF centres submit data annually to Canadian Cystic Fibrosis Registry, which tracks lung function, hospital admissions, and CF drug use. Thus, there is the possibility of tracking real-world impact of LUM/IVA in this population over time.

5. CONCLUSIONS

The CDR systematic review included two phase 3 RCTs (TRAFFIC [N=559] and TRANSPORT [N=563]) that investigated the comparative safety and efficacy of LUM/IVA in patients with CF who were 12 years and older with mild to moderate lung disease and who were homozygous for the F508del-CFTR mutation. Both studies demonstrated that 24 weeks of treatment with LUM/IVA was associated with statistically significant improvements in $ppFEV_1$ (absolute increases of 2.6% to 3.0% and relative increases of 4.3% to 4.5%); however, the clinical significance of the improvements is uncertain. An ongoing extension study (PROGRESS) demonstrated that the improvements in $ppFEV_1$ persisted after 48 weeks of treatment. Compared with placebo, LUM/IVA demonstrated clinically meaningful reductions in the number and severity of pulmonary exacerbations, including those that required hospitalization and treatment with IV antibiotics; however, no conclusions about the statistical significance of these outcomes could be made. There was inconsistency in the results for changes in BMI, with statistical significance being demonstrated in only the TRANSPORT trial. A pre-planned pooled analysis; however, suggests that treatment with LUM/IVA was associated with improvements in BMI, although the magnitude of improvement was of uncertain clinical significance. Treatment with LUM/IVA was not associated with statistically significant or clinically relevant improvements in health-related quality of life.

LUM/IVA was generally well tolerated in the study populations, with more than 95% of LUM/IVA-treated patients completing the 24-week treatment period. LUM/IVA was associated with an increased frequency of respiratory adverse events (e.g., dyspnea and abnormal respiration) compared with placebo; however, these events were typically mild to moderate in severity and occurred shortly after the initiation of treatment.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One patient group, Cystic Fibrosis Canada (CF Canada), responded to the CADTH Common Drug Review (CDR) call for patient input. CF Canada is a charitable non-profit corporation with a mission to help people with CF. CF Canada funds research toward finding a cure and improving control of CF, supports high-quality CF care, and promotes public awareness of CF. CF Canada has received financial contributions from pharmaceutical companies including Mylan, Gilead, Hoffman-La Roche, Merck, Insmed, and Vertex, as well as Innovative Medicines Canada. Contributions from pharmaceutical companies accounted for less than 2% of the organization's gross revenue in 2015-2016. CF Canada declared no conflicts of interest in the preparation of this submission.

2. Condition-Related Information

Information was gathered through input from CF patients and their families with the assistance of CF clinics and through the use of social media. CF Canada's national patient data registry was also a source of information.

Currently, there are 4,000 Canadians living with CF, an inherited genetic disorder primarily affecting the lungs and digestive system. The disease causes the body to produce thick, sticky mucus, which is difficult to clear from the lungs, resulting in persistent infections, progressive scarring of the airways, and a decline in lung function. Additionally, the mucus clogs the pancreas, preventing digestive enzymes from getting to the intestine. As a result, approximately 85% of CF patients also struggle to digest fats, proteins, and nutrients. Lack of nutrition prevents normal growth and development in babies and children. Unhealthy weight loss and difficulty gaining or maintaining weight are common problems for many people of all ages who have CF.

Respiratory failure is the primary cause of death in CF patients. Of the 40 CF patients who died in 2013, half were younger than 35 years of age.

Managing CF requires a demanding treatment routine with regular visits to specialized CF clinics. CF treatments, CF-related infections, and hospitalizations take a toll on patients' emotional stamina and have a significant impact on their day-to-day quality of life, affecting life decisions that include education, career, travel, relationships, and family planning. The fear of having a life-threatening disease can be overwhelming, as they face the insecurity of what the disease may hold for the future. They often have limited physical abilities and do not have the energy to enjoy time with their families and friends, to complete their education, maintain employment, or travel. Daily treatment for CF is an exhausting and frustrating exercise. If a patient's condition worsens, a hospital stay of at least two weeks may be required and there may be a need for oxygen therapy at some point. One patient reported that she has been hospitalized approximately three times per year for 20 years.

Being a caregiver for a CF patient can have significant emotional, psychological, physical, and financial impacts. Caregivers may feel helpless and devastated, watching their loved ones cope with a life-threatening disease. Hospitalizations and treatments that may consume two to seven hours a day disrupt family routines. Caregivers may also have to change their social activities and their employment in order to accommodate treatment of a loved one with CF. Caregivers reported incurring repetitive strain injuries while assisting with physical therapies for CF.

3. Current Therapy-Related Information

Most CF patients take pancreatic enzymes, multivitamins and nutritional supplements daily to maintain normal growth. Patients also perform airway clearance techniques, which include physiotherapy and exercises, at least twice a day for about 30 to 45 minutes per session to improve the clearance of secretions from their lungs. Inhaled medications are also used daily to open the airways. In addition, inhaled, intravenous, or oral antibiotic treatments are used to control infections. Persistent infections eventually destroy the lungs and, while lung transplantation may help end-stage CF patients, the extended median life expectancy is only 34 months following a lung transplant.

Statistics from the 2013 Canadian Cystic Fibrosis Registry Annual Report showed that CF patients spent a cumulative total of almost 25,000 days in hospital, attended more than 16,500 clinic visits, and underwent 676 courses of home intravenous therapy.

4. Expectations About the Drug Being Reviewed

Patients who had not been treated with LUM/IVA expect it to improve their health and quality of life, by improving lung function, avoiding the need for lung transplantation, and helping them gain weight. They expect LUM/IVA will reduce the frequency of pulmonary exacerbations and decrease their need for antibiotics.

Patients who have experience with LUM/IVA reported that it delayed the progression of CF much more effectively than current conventional therapies by improving lung function, weight gain, energy, and reducing the risk of exacerbations. Treatment-experienced patients also reported that the clinical benefits of treatment with LUM/IVA were apparent in a relatively short period of time. Patients reported that treatment with LUM/IVA improved their health, quality of life, and their ability to complete day-to-day activities. These patients expressed satisfaction with LUM/IVA and indicated that they cannot picture their lives without this treatment.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 25, 2016
Alerts:	Bi-weekly search updates until June 15, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY

#	Searches
1	S900006790.rn,nm.
2	(orkambi* or "ivacaftor/lumacaftor" or "lumacaftor/ivacaftor").ti,ab,ot,kf,hw,rn,nm.
3	or/1-2
4	873054-44-5.nm,rn.

MULTI-DATABASE STRATEGY	
#	**Searches**
5	(ivacaftor* or kalydeco* or VX770 or VX 770).ti,ab,ot,kf,hw,rn,nm.
6	or/4-5
7	936727-05-8.nm,rn.
8	(lumacaftor* or VRT 826809 or VRT826809 or VX809 or VX 809).ti,ab,ot,kf,hw,rn,nm.
9	or/7-8
10	6 and 9
11	3 or 10
12	11 use pmez
13	*ivacaftor plus lumacaftor/
14	(orkambi* or "ivacaftor/lumacaftor" or "lumacaftor/ivacaftor").ti,ab,kw.
15	or/13-14
16	*ivacaftor/
17	(ivacaftor* or kalydeco* or VX770 or VX 770).ti,ab,kw.
18	or/16-17
19	*lumacaftor/
20	(lumacaftor* or vrt 826809 or vrt826809 or vx 809 or vx809).ti,ab,kw.
21	or/19-20
22	18 and 21
23	15 or 22
24	23 use oemezd
25	conference abstract.pt.
26	24 not 25
27	12 or 26
28	exp animals/
29	exp animal experimentation/ or exp animal experiment/
30	exp models animal/
31	nonhuman/
32	exp vertebrate/ or exp vertebrates/
33	or/28-32
34	exp humans/
35	exp human experimentation/ or exp human experiment/
36	or/34-35
37	33 not 36
38	27 not 37

MULTI-DATABASE STRATEGY	
#	**Searches**
39	remove duplicates from 38

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	February 2016
Keywords:	Orkambi, ivacaftor AND lumacaftor
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Boyle et al., 2014[63]	The CDR systematic review protocol excludes phase 2 RCTs unless they are considered to be pivotal for regulatory filing.
PROGRESS[64]	The CDR systematic review protocol limits inclusion to published and unpublished RCTs; therefore, the PROGRESS study was excluded from the review and summarized as a supplemental issue. Key data from the PROGRESS study are summarized in Appendix 6.

CDR = CADTH Common Drug Review; RCT = randomized controlled trial.

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 23: CHANGE IN ppFEV$_1$ AT EACH STUDY VISIT IN TRAFFIC AND TRANSPORT

Study	Time	LS Mean (SE)[a]		LUM/IVA vs. Placebo	
		Placebo	LUM/IVA	LSMD (95% CI)[a]	*P* value
Absolute change in ppFEV$_1$					
TRANSPORT	Baseline	60.45 (13.22)	60.48 (14.29)	—	—
	Day 15	[redacted]	[redacted]	[redacted]	[redacted]
	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 16	[redacted]	[redacted]	[redacted]	[redacted]
	Week 24	–0.02 (0.590)	2.63 (0.593)	2.65 (1.06, 4.24)	0.0011
TRAFFIC	Baseline	60.37 (14.32)	60.59 (14.01)	—	—
	Day 15	[redacted]	[redacted]	[redacted]	[redacted]
	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 16	[redacted]	[redacted]	[redacted]	[redacted]
	Week 24	–0.73 (0.590)	1.68 (0.598)	2.41 (0.80, 4.02)	0.0034
Relative change in ppFEV$_1$					
TRANSPORT	Baseline	60.37 (14.32)	60.59 (14.01)	—	—
	Day 15	[redacted]	[redacted]	[redacted]	[redacted]
	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 16	[redacted]	[redacted]	[redacted]	[redacted]
	Week 24	0.16 (1.027)	4.85 (1.031)	4.69 (1.94, 7.45)	0.0009
TRAFFIC	Baseline	60.45 (13.22)	60.48 (14.29)	—	—
	Day 15	[redacted]	[redacted]	[redacted]	[redacted]
	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 16	[redacted]	[redacted]	[redacted]	[redacted]
	Week 24	–0.85 (0.994)	3.30 (1.009)	4.15 (1.44, 6.86)	0.0028

CI = confidence interval; LS = least squares; LSMD = least squares mean difference; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients with events; MMRM = mixed-effects model for repeated measures; ppFEV$_1$ = per cent predicted forced expiratory volume in 1 second; q12h = every 12 hours; SE = standard error; vs. = versus.

[a] MMRM model included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 versus ≥ 18 years), and ppFEV$_1$ severity at screening (< 70% versus ≥ 70%).[12,13]

Source: Clinical Study Reports for TRAFFIC[12] and TRANSPORT.[13]

TABLE 24: SUBGROUP ANALYSES FOR ppFEV$_1$ FROM TRAFFIC AND TRANSPORT

Subgroup	Least Squares Mean Difference (95% CI)[a]			
	Absolute Change in ppFEV$_1$		Relative Change in ppFEV$_1$	
	TRAFFIC	TRANSPORT	TRAFFIC	TRANSPORT
Age				
≥ 12 to < 18 years	4.12 (0.75 to 7.50)	1.66 (−1.95 to 5.27)	[redacted]	[redacted]
≥ 18 years	2.02 (0.55 to 3.50)	3.46 (1.92 to 4.99)	[redacted]	[redacted]
ppFEV$_1$ at screening				
< 70%	2.95 (1.33 to 4.57)	2.95 (1.33 to 4.57)	[redacted]	[redacted]
≥ 70%	2.19 (−0.81 to 5.19)	2.19 (−0.81 to 5.19)	[redacted]	[redacted]
ppFEV$_1$ at baseline				
< 40%	[redacted]	[redacted]	[redacted]	[redacted]
≥ 40%	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; FAS = full analysis set; LA = long-acting bronchodilator; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; MMRM = mixed-effects model for repeated measures; ppFEV$_1$ = per cent predicted forced expiratory volume in 1 second; q12 = every 12 hours; SA = short-acting bronchodilator.

[a] MMRM model included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 versus ≥ 18 years), and ppFEV$_1$ severity at screening (< 70% versus ≥ 70%).[12,13]

TABLE 25: SENSITIVITY ANALYSES FOR ppFEV$_1$ FROM TRAFFIC AND TRANSPORT

Analysis	Study	Parameter	Placebo	LUM/IVA
MMRM with on-treatment measurements only[a]	TRAFFIC	BL; mean (SD)	60.45 (13.221)	60.48 (14.289)
		LSM change (SE)	[redacted]	[redacted]
		LSMD (95% CI)	[redacted]	
		P value	[redacted]	
	TRANSPORT	BL; mean (SD)	60.37 (14.318)	60.59 (14.014)
		LSM change (SE)	[redacted]	[redacted]
		LSMD (95% CI)	[redacted]	
		P value	[redacted]	
ANCOVA with multiple imputation[b]	TRAFFIC	LSMD (SE)	[redacted]	
		P value	[redacted]	
	TRANSPORT	LSMD (SE)	[redacted]	
		P value	[redacted]	

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; LUM/IVA = lumacaftor/ivacaftor; MMRM = mixed-effects model for repeated measures; SD = standard deviation; SE = standard error.

[a] MMRM model included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 versus ≥ 18 years), and ppFEV$_1$ at screening (< 70% versus ≥ 70%).

[b] ANCOVA model included treatment, sex, age at baseline (< 18 versus ≥ 18 years), and ppFEV$_1$ at screening (< 70% versus ≥ 70%).

TABLE 26: SUBGROUP ANALYSES FOR PULMONARY EXACERBATIONS FROM TRAFFIC AND TRANSPORT

Subgroup	Endpoints	TRAFFIC		TRANSPORT	
		Placebo	LUM/IVA	Placebo	LUM/IVA
Age					
≥ 12 to < 18 years	Events (per year)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate ratio (95% CI)	[redacted]		[redacted]	
≥ 18 years	Events (per year)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate ratio (95% CI)	[redacted]		[redacted]	
$ppFEV_1$ at screening					
< 70%	Events (per year)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate ratio (95% CI)	[redacted]		[redacted]	
≥ 70%	Events (per year)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate ratio (95% CI)	[redacted]		[redacted]	
$ppFEV_1$ at baseline					
< 40%	Events (per year)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate ratio (95% CI)	[redacted]		[redacted]	
≥ 40%	Events (per year)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate ratio (95% CI)	[redacted]		[redacted]	

CI = confidence interval; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; q12h = every 12 hours.
Note: Treatment comparison was carried out using regression analysis for a negative binomial distribution with sex (male versus female), age group (< 18 versus ≥ 18 years old), and $ppFEV_1$ at screening (< 70% versus ≥ 70%) as covariates with the logarithm of time on study as the offset.[12,13]
Source: Clinical Study Reports for TRAFFIC[12] and TRANSPORT.[13]

TABLE 27: SUMMARY OF ADVERSE EVENTS FROM TRAFFIC AND TRANSPORT

AEs, n (%)	TRAFFIC		TRANSPORT	
	Placebo	LUM/IVA	Placebo	LUM/IVA
Summary of AEs				
Any AEs	174 (94.6)	174 (95.6)	181 (97.3)	177 (94.7)
Serious adverse events	49 (26.6)	33 (18.1)	57 (30.6)	31 (16.6)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs	4 (2.2)	6 (3.3)	2 (1.1)	11 (5.9)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most Common AEs (≥ 10% Patients)				
Infective pulmonary exacerbation	87 (47.3)	67 (36.8)	95 (51.1)	65 (34.8)
Cough	66 (35.9)	48 (26.4)	82 (44.1)	56 (29.9)
Headache	25 (13.6)	29 (15.9)	33 (17.7)	29 (15.5)
Hemoptysis	24 (13.0)	30 (16.5)	26 (14.0)	20 (10.7)
Diarrhea	13 (7.1)	24 (13.2)	18 (9.7)	21 (11.2)
Respiration, abnormal	9 (4.9)	14 (7.7)	13 (7.0)	18 (9.6)
Sputum, increased	23 (12.5)	25 (13.7)	47 (25.3)	29 (15.5)
Dyspnea	14 (7.6)	17 (9.3)	15 (8.1)	31 (16.6)
Nasopharyngitis	20 (10.9)	26 (14.3)	20 (10.8)	22 (11.8)
Oropharyngeal pain	10 (5.4)	11 (6.0)	20 (10.8)	13 (7.0)
Abdominal pain	12 (6.5)	23 (12.6)	20 (10.8)	10 (5.3)
Fatigue	19 (10.3)	17 (9.3)	10 (5.4)	17 (9.1)
Nausea	11 (6.0)	14 (7.6)	17 (9.1)	32 (17.1)
Pyrexia	12 (6.5)	17 (9.3)	22 (11.8)	16 (8.6)
Nasal congestion	25 (13.6)	11 (6.0)	19 (10.2)	13 (7.0)
Upper respiratory tract infection	10 (5.4)	17 (9.3)	10 (5.4)	20 (10.7)
WDAEs				
WDAEs	4 (2.2)	6 (3.3)	2 (1.1)	11 (5.9)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; CF = cystic fibrosis; CPK = creatine phosphokinase; LUM/IVA = lumacaftor 400 mg q12h + IVA 250 mg q12h; n = number of patients with events; q12h = every 12 hours; WDAE = withdrawal due to adverse event.
Sources: Wainwright et al., 2015;[14] Common Technical Document section 2.7.4;[15] and Clinical Study Reports for TRAFFIC[12] and TRANSPORT.[13]

TABLE 28: RESPIRATORY ADVERSE EVENTS BY FEV_1 AT BASELINE (A) OR SCREENING (B)

[redacted]

FEV_1 = forced expiratory volume in 1 second; LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients with events; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; q12h = every 12 hours.
Source: Common Technical Document section 2.7.4.[15]

[redacted]

LUM/IVA = lumacaftor 400 mg q12h + ivacaftor 250 mg q12h; n = number of patients with events; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; q12 = every 12 hours.
Source: Common Technical Document section 2.7.4.[15]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To summarize the validity and minimal clinically important differences (MCIDs) of the following outcome measures:

- Forced expiratory volume in one second (FEV_1)
- Cystic Fibrosis Questionnaire–Revised (CFQ-R)
- EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D).

Findings

Forced Expiratory Volume in One Second

FEV_1 is the maximal amount of air forcefully exhaled in one second, expressed in litres.[65] The measured volume is converted to a percentage of predicted normal value, which is adjusted based on age, sex, and body composition.[65] FEV_1 is used to establish the severity of lung disease (normal or mild pulmonary dysfunction, > 70% predicted; moderate dysfunction, 40% to 69% predicted; and severe dysfunction, < 40% predicted), tracking changes in lung function over time, and in evaluating the effectiveness of therapeutic interventions in cystic fibrosis (CF).[65,66]

FEV_1 is a commonly used end point for clinical trials of obstructive lung diseases including CF[67] and is the preferred end point in the European Medicines Agency (EMA) guidance document on the development of therapeutic drugs for CF, based on the fact that the main pulmonary defect in CF is obstructive.[66] FEV_1 has been shown to relate to morbidity, disease progression, and mortality in CF, making it a meaningful surrogate marker for survival.[67]

However, there are limitations with the use of FEV_1 for patients with CF:

- The manoeuvre required to assess FEV_1 is highly dependent on patient cooperation and effort:
  - The test (spirometry) should be repeated at least three times to ensure reproducibility.[65]
  - Spirometry can be used only on children old enough to comprehend and follow the instructions given (six years old or more), and only on patients who are able to understand and follow instructions.[66,67]
  - FEV_1 can generally only be underestimated. The only exception in which FEV_1 can be overestimated is in individuals with some diseases where a softer exhalation can reduce the spasm or collapse of lung tissue, thereby artificially elevating the measure.
- FEV_1 decline is only meaningful over time and is subject to seasonal and environmental effects.[67]
- There are no published data on the magnitude of change in FEV_1 that is clinically meaningful.[67]
- CF is a multi-organ disease and FEV_1 measures only lung health.[67]
- FEV_1 improvement has a ceiling effect for patients with mild lung impairment.[67]
- There are no published minimal clinically important differences (MCIDs) for FEV_1 in patients with CF.

The EMA suggests a study duration of six months for the demonstration of efficacy on respiratory function (based on repeated measurements of FEV_1) with a 12-month follow-up for safety.[66]

Cystic Fibrosis Questionnaire–Revised

The CFQ-R is a disease-specific quality of life (QoL) instrument designed for patients with CF, consisting of age-appropriate versions for children aged six to 13 years (CFQ-C) and their parents (who serve as a proxy for their child; CFQ-P), and individuals ≥ 14 years of age (CFQ-14).[68] It consists of three modules: a QoL module containing both generic (physical functioning, energy, emotional, social limitations, role limitations) and disease-specific domains (body image, eating disturbances, treatment constraints); a symptoms module with three symptom scales (respiratory, digestive, and weight); and a health perception module. Items are summed to generate a domain score and standardized; scores range from 0 to 100, with higher scores indicating better QoL. The scales are designed to measure functioning during the two-week period prior to administration of the CFQ-R.[69]

Several studies have evaluated the validity and reliability of the CFQ-R questionnaire.[70-72] Quittner et al.[70] examined the psychometric properties of the CFQ-R using data from the Epidemiologic Study of Cystic Fibrosis, a national US multi-centre longitudinal cohort study containing CFQ-R and health outcomes data from 7,330 patients aged six to 70 years. They reported adequate internal consistency (Cronbach alpha ≥ 0.70) for most domains and scales on each of the three versions. The CFQ was sensitive to changes in QoL associated with increasing disease severity (based on pulmonary function, FEV_1); this analysis was limited, however, because the CFQ-C had less variability in disease severity as few school-age children had a FEV_1 < 70% predicted. Quittner et al.[70] also reported fair to moderate agreement between the child and parent versions on all scales (intraclass correlation coefficient range, 0.26 to 0.56); however, stronger agreement was found on domains that measured more observable signs and symptoms, such as physical functioning, eating problems, and respiratory symptoms. There was fair to moderate convergence between CFQ-R scales and health outcomes, including per cent predicted FEV_1 ($ppFEV_1$; correlation range, 0.25 to 0.51), number of pulmonary exacerbations treated with intravenous (IV) antibiotics (range, −0.23 to −0.35), and body mass index (BMI) (range, 0.22 to 0.44). The strongest correlations were demonstrated for the physical functioning and respiratory domains with $ppFEV_1$ (range: 0.33 to 0.51 and 0.32 to 0.42, respectively) and for the weight scale and BMI (r = 0.42 and 0.44 on the CFQ-P and CFQ-14, respectively). Overall, the correlations were lower for the CFQ-C and CFQ-P versus the CFQ-14. Test–retest reliability was assessed previously (repeat administration over 14 days) and intraclass correlation coefficients were estimated to range from 0.45 to 0.90 on all scales.[71]

A previous study[71] also showed that the CFQ-R correlated well with the Short Form (36) Health Survey (SF-36). Correlations were moderate to strong (r = 0.42 to 0.57) between similar dimensions of the CFQ and SF-36 (physical, health perceptions/general health, vitality, role/role physical, emotional functioning/mental health, and social) and weak to moderate (r = 0.19 to 0.42) between scales not expected to be related (digestion and role scales of the CFQ and general health and mental health scales of the SF-36).

The MCID was estimated using the CFQ-R–respiratory symptom scale in two study populations: one with patients with stable CF and chronic *Pseudomonas aeruginosa* airway infection; the other with patients with exacerbation of CF and chronic *P. aeruginosa* airway infection.[69] Both anchor-based and distribution-based methods were used. The MCID, or the smallest change a patient could detect in terms of changes in respiratory symptoms, for patients with stable disease was determined to be 4.0, and for patients with exacerbation, 8.5.[69]

The main limitations of the CFQ-R are ceiling effects for certain scales (notably, the eating problems scale), potential difficulty for patients to understand some of the items (e.g., CFQ-R-Respiratory, item

"trouble breathing"), and concerns that a patient may not be able to distinguish between some of the response items on the scale (e.g., response choices such as "somewhat" versus "a little").[67,70]

EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire

The EQ-5D[73,74] is a generic QoL instrument that has been applied to a wide range of health conditions and treatments including CF. The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3), representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[73,74] The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state," respectively. Respondents are asked to rate their own health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their own health on that day. Hence, the EQ-5D produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
2. A population preference-weighted health index score based on the descriptive system
3. A self-reported assessment of health status based on the EQ-VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively.

The MCID for the EQ-5D ranges from 0.033 to 0.074.[36] The validity and MCID of the EQ-5D have not been formally assessed in CF.

Conclusion

FEV_1 and CFQ-R are commonly used, validated, and reliable outcome measures in clinical trials of patients with CF. The reported MCID for the CFQ-R–respiratory symptom scale varies from 4.0 to 8.5, depending on patient disease status (stable versus acute exacerbation). The MCID for the EQ-5D ranges from 0.033 to 0.074. No MCID was found for FEV_1.

APPENDIX 6: SUMMARY OF THE PROGRESS EXTENSION STUDY

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

1. Objective

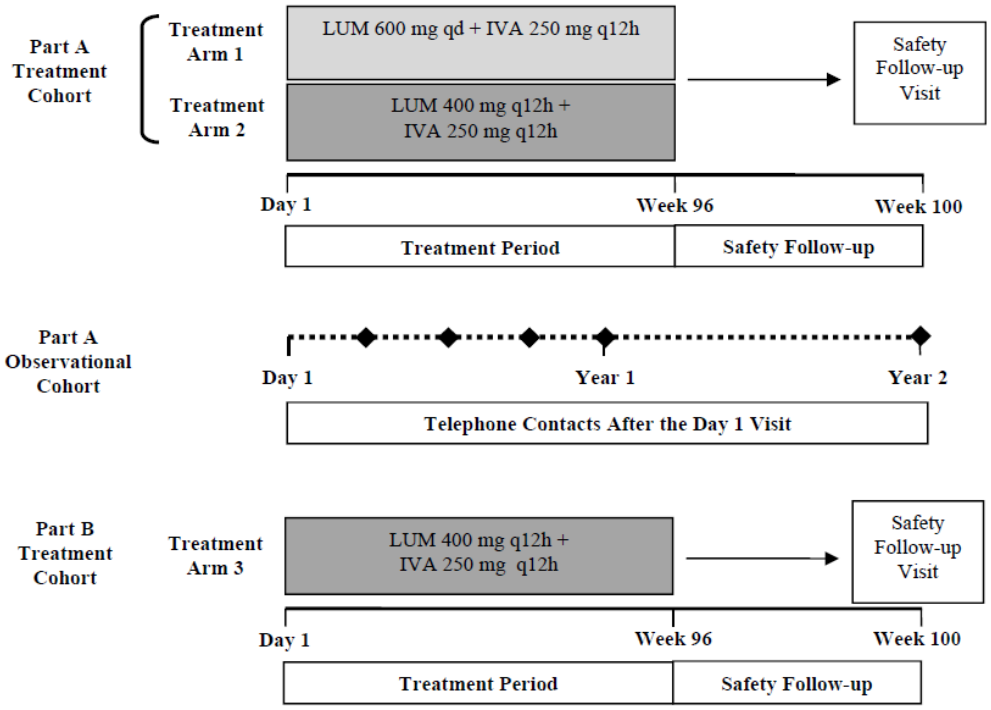
To summarize the PROGRESS study, which evaluated the long-term safety, tolerability, and efficacy of lumacaftor (LUM) in combination with ivacaftor (IVA) in patients aged 12 years and older with cystic fibrosis (CF), homozygous or heterozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Findings

Study Design

PROGRESS is a phase 3, parallel-group, multi-centre, rollover study that consisted of two parts, as depicted in Figure 10. Part A included two treatment groups and an observational group, whereas Part B included only one treatment group. For the purpose of this summary, only the Part A treatment group 2 will be discussed. The Part A treatment group 1 is excluded from this summary as the dose utilized in the treatment is not approved by Health Canada. The Part A observational group is also excluded from this summary, as the participants in this group did not receive any dosing of LUM in combination with IVA during PROGRESS. Finally, the Part B treatment group was also excluded from this summary, as it recruited participants from cohort 4 from Study 102, who were exclusively heterozygous for the F508del-CFTR mutation.

Figure 10: DESIGN OF THE PROGRESS EXTENSION STUDY



IVA = ivacaftor; LUM = lumacaftor; q12h = every 12 hours; qd = once daily.
Source: Reproduced from Clinical Study Report for PROGRESS.[64]

Patients participating in TRAFFIC and TRANSPORT were eligible to participate in the Part A treatment group 2 of PROGRESS if they met the following criteria:

- Aged 12 years and older
- Confirmed diagnosis of CF and were homozygous for the F508del-CFTR mutation
- Completed 24 weeks of study drug treatment in TRAFFIC, TRANSPORT, or cohort 4 of Study 102
- Had study drug interruptions, but completed study visits up to week 24 of TRAFFIC or TRANSPORT. Patients who were not taking study drug at the week 24 visit, including patients who required study drug interruption to be either continued or initiated at day 1 in PROGRESS, were required to have the manufacturer's approval for enrolment or randomization in the Part A treatment cohort.

The Part A treatment group 2 consisted of a 96-week double-blind treatment period in which patients and investigators remained blinded to the treatment. Patients treated with placebo in TRAFFIC or TRANSPORT started a dose-blinded treatment of 400 mg lumacaftor every 12 hours in combination with 250 mg ivacaftor every 12 hours (LUM/IVA) in PROGRESS. These patients were randomized using a 1:1 ratio to one of the two treatment groups in Part A (treatment group 1 and treatment group 2). Randomization was stratified by age (< 18 versus ≥ 18 years), sex (male versus female), and per cent predicted forced expiratory volume in one second ($ppFEV_1$) severity (< 70% versus ≥ 70% predicted) collected at baseline or the last non-missing value prior to receiving LUM/IVA. Patients treated with LUM/IVA in TRAFFIC and TRANSPORT remained dose-blinded and continued to receive the same dose they received during the pivotal studies. The treatment period was followed by a 4-week safety follow-up period. Data from 24-week interim analysis are summarized in this report (i.e., 24 weeks into the PROGRESS study).

Assessment

Safety was assessed by monitoring adverse events, clinical laboratory assessments, physical examinations, vital signs, electrocardiograms, pulse oximetry, and spirometry. Efficacy assessment was derived from spirometry, height, weight, body mass index (BMI), Cystic Fibrosis Questionnaire–Revised (CFQ-R), and pulmonary exacerbations.

Efficacy analyses were conducted using the cumulative study period, defined as the period beginning from the initial dose of study drug in the pivotal studies (TRAFFIC or TRANSPORT) to the data cut-off (week 24 in PROGRESS). Safety analyses were conducted using the active treatment period, defined as the period beginning from the initial dose of active treatment to the data cut-off (week 24 in PROGRESS). Data were analyzed in 24-week blocks starting with the first dose of LUM/IVA. The first 24-week block utilizes data from TRAFFIC and TRANSPORT (0 to 24 weeks) and the subsequent 24-week block (24 to 48 weeks) utilizes data from PROGRESS. Data were also analyzed for patients with more than 48 weeks of exposure to LUM/IVA.

Two approaches were used to analyze the efficacy data in the 0-to-24-week block and the 24-to-48-week block using different baselines for evaluating change. The first approach evaluated change in efficacy data in the 0-to-24-week block using baselines evaluated in TRAFFIC and TRANSPORT for both the study drug and the placebo group. The second approach evaluated change in efficacy data in the 24-to-48-week block using baselines evaluated in TRAFFIC and TRANSPORT for the study drug group. For patients who had received placebo in the previous study, changes in efficacy data were examined using the last non-missing measurement prior to receiving treatment in PROGRESS as a baseline.

Results

[redacted] Patient demographics and baseline characteristics are detailed in Table 29 and are similar across the previous studies and between treatment groups in PROGRESS. Patient disposition is detailed in Table 30.

TABLE 29: BASELINE CHARACTERISTICS FROM TRAFFIC, TRANSPORT, AND PROGRESS (FULL ANALYSIS SET)

Category	Planned Treatment	
	LUM/IVA, n (%)	Pbo then LUM/IVA, n (%)
Number, N	**340**	**176**
Sex		
Male	176 (51.8)	90 (51.1)
Female	164 (48.2)	86 (48.9)
Age, years		
Mean (SD)	25.1 (9.3)	24.9 (10.1)
Median (range)	24.0 (12, 57)	23.0 (12, 64)
12 to < 18	94 (27.6)	47 (26.7)
≥ 18	246 (72.4)	129 (73.3)
Race		
White	335 (98.5)	174 (98.9)
Black	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Region		
North America	[redacted]	[redacted]
Europe	[redacted]	[redacted]
Australia	[redacted]	[redacted]
Weight kg mean (SD)	[redacted]	[redacted]
BMI kg/m^2 mean (SD)	[redacted]	[redacted]
$ppFEV_1$, %		
Mean (SD)	60.4 (14.2)	60.2 (13.8)
Min, max	31.3, 96.5	33.9, 99.8
< 40	29 (8.5)	10 (5.7)
≥ 40 to < 70	213 (62.6)	120 (68.2)
≥ 70 to ≤ 90	91 (26.8)	42 (23.9)
> 90	3 (0.9)	2 (1.1)

Category	Planned Treatment	
	LUM/IVA, n (%)	Pbo then LUM/IVA, n (%)
FEV_1, L		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second; LUM/IVA = 400 mg lumacaftor q12h + 250 mg ivacaftor q12h; Pbo then LUM/IVA = placebo in pivotal study and 400 mg lumacaftor q12h + 250 mg ivacaftor q12h in Study 105; min = minimum; max = maximum; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; q12h = every 12 hours; SD = standard deviation.
Note: Baseline characteristics are based on the start of TRAFFIC and TRANSPORT.[64]
Source: Clinical Study Report for PROGRESS.[64]

TABLE 30: PATIENT DISPOSITION — STUDY 105

Category	Planned Treatment	
	LUM/IVA, n (%)	Pbo then LUM/IVA, n (%)
All patients	**341**	**176**
Randomized but not dosed	1	0
Full analysis set	340	176
Safety analysis set	[redacted]	[redacted]
Completed treatment	0	0
Treatment ongoing	309 (90.9)	158 (89.8)
Discontinued treatment	31 (9.1)	18 (10.2)
AE	9 (2.6)	10 (5.7)
Refused dosing (not due to AE)	[redacted]	[redacted]
Lost due to follow-up	[redacted]	[redacted]
Non-compliance with study drug	[redacted]	[redacted]
Other non-compliance	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]
Required prohibited medication	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]
Other	[redacted]	[redacted]
Last scheduled on-treatment visit		
Extension day 1	[redacted]	[redacted]
Extension day 15	[redacted]	[redacted]
Extension week 4	[redacted]	[redacted]
Extension week 8	[redacted]	[redacted]
Extension week 12	[redacted]	[redacted]
Extension week 16	[redacted]	[redacted]
Extension week 20	[redacted]	[redacted]
Extension week 24	[redacted]	[redacted]
Extension week 28	[redacted]	[redacted]
Extension week 32	[redacted]	[redacted]
Extension week 36	[redacted]	[redacted]
Extension week 40	[redacted]	[redacted]
Extension week 44	[redacted]	[redacted]

Category	Planned Treatment	
	LUM/IVA, n (%)	Pbo then LUM/IVA, n (%)
Extension week 48	[redacted]	[redacted]
Extension week 52	[redacted]	[redacted]
Extension week 56	[redacted]	[redacted]
Extension week 60	[redacted]	[redacted]
No scheduled on-treatment visit	[redacted]	[redacted]

AE = adverse event; LUM/IVA = 400 mg lumacaftor q12h + 250 mg ivacaftor q12h; Pbo then LUM/IVA = placebo in pivotal study and 400 mg lumacaftor q12h + 250 mg ivacaftor q12h in PROGRESS; q12h = every 12 hours.
Source: Clinical Study Report for PROGRESS[64]

Safety

Ninety-eight per cent of patients experienced at least one adverse event (532 of the 544 throughout TRAFFIC, TRANSPORT, and PROGRESS detailed in Table 31), with the most common ([redacted] of patients) being infective pulmonary exacerbation of CF, cough, headache, sputum increase, dyspnea, hemoptysis, and nasopharyngitis. Detailed data of the most common (≥ 5% of patients) adverse events are presented in Table 32. The most common serious adverse events (SAEs) were infective pulmonary exacerbation of CF, hemoptysis, and distal intestinal obstruction syndrome, occurring in 19.5%, 2.0%, and 1.1% of patients, respectively (Table 31). In total, 6.3% of patients withdrew due to adverse events (Table 31). A total of [redacted] of patients experienced hepatic adverse events and [redacted] of patients withdrew due to liver-related adverse events. A total of [redacted] of patients experienced at least one respiratory adverse event and [redacted] of patients withdrew as a result of respiratory-related adverse events. Detailed data with regard to adverse events of special interest are presented in Table 33 and Table 34.

Generally, adverse events were similar across the pivotal studies and PROGRESS. However, CF-related events continued to increase with time. Infective pulmonary exacerbations of CF were reported for 46.9% of patients in PROGRESS. Cough, sputum increase, and hemoptysis occurred in 38.8%, 21.3%, and 19.1% of patients in PROGRESS. In terms of serious adverse events, the proportion of infective pulmonary exacerbations of CF occurred in 19.5% of patients in PROGRESS. With respect to notable respiratory and reactive airways adverse events, incidences in PROGRESS were [redacted] and [redacted]. Withdrawal due to adverse events and notable hepatic adverse events remained similar across PROGRESS and the previous studies.

TABLE 31 : SUMMARY OF ADVERSE EVENTS CUMULATIVE TO WEEK 48

Summary of AEs	0 to 48 weeks, N = 544
	LUM/IVA, n (%)
AEs	
Any AEs	532 (97.8)
AEs leading to discontinuation	34 (6.3)
AEs leading to interruption	[redacted]
Grade 3 or 4 AEs	100 (18.4)
Serious AEs	159 (29.2)
AEs leading to death	[redacted]
SAEs	
Any SAEs	159 (29.9)
Infective pulmonary exacerbation of CF	106 (19.5)
Pneumonia	[redacted]
Hemoptysis	11 (2.0)
Respiration, abnormal	[redacted]
Pneumothorax	[redacted]
Distal intestinal obstruction syndrome	6 (1.1)
Small intestinal obstruction	[redacted]
Blood creatine phosphokinase, increased	[redacted]
Forced expiratory volume, decreased	[redacted]
Liver function test abnormal	[redacted]
WDAEs	
Any WDAEs	34 (6.3)
Respiration, abnormal	[redacted]
Dyspnea	[redacted]
Hemoptysis	[redacted]
Bronchospasms	[redacted]
Blood creatine phosphokinase, increased	[redacted]
Forced expiratory volume, decreased	[redacted]
Diarrhea	[redacted]
Infective pulmonary exacerbation of CF	[redacted]

AE = adverse event; CF = cystic fibrosis; LUM/IVA = 400 mg lumacaftor q12h + 250 mg ivacaftor q12h; q12h = every 12 hours; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Note: Data are cumulative and include AEs from TRAFFIC and TRANSPORT as well as PROGRESS.
Source: Clinical Study Report for PROGRESS.[64]

TABLE 32: MOST COMMON ADVERSE EVENTS (≥ 5%) CUMULATIVE TO WEEK 48

AEs	0 to 48 weeks, N = 544
	LUM/IVA, n (%)
Any AEs	532 (97.8)
Infective pulmonary exacerbation of CF	255 (46.9)
Cough	211 (38.8)
Headache	88 (16.2)
Sputum, increased	116 (21.3)
Dyspnea	89 (16.4)
Hemoptysis	104 (19.1)
Diarrhea	77 (14.2)
Nausea	72 (13.2)
Respiration, abnormal	74 (13.6)
Nasopharyngitis	81 (14.9)
Oropharyngeal pain	57 (10.5)
Pyrexia	65 (11.9)
Fatigue	57 (10.5)
Upper respiratory tract infection	70 (12.9)
Abdominal pain	55 (10.1)
Nasal congestion	53 (9.7)
Viral upper respiratory tract infection	[redacted]
Rhinitis	[redacted]
Flatulence	[redacted]
Blood creatine phosphokinase, increased	[redacted]
Rash	[redacted]
Sinusitis	[redacted]
Rhinorrhea	[redacted]
Vomiting	[redacted]
Abdominal pain, upper	[redacted]
Constipation	[redacted]
Bacterial test positive	[redacted]

AE = adverse event; CF = cystic fibrosis; LUM/IVA = 400 mg lumacaftor q12h + 250 mg ivacaftor q12h; q12h = every 12 hours.
Note: Data are cumulative and include AEs from TRAFFIC and TRANSPORT as well as PROGRESS.
Source: Clinical Study Report for PROGRESS.[64]

TABLE 33: HEPATIC ADVERSE EVENTS CUMULATIVE TO WEEK 48

Hepatic AEs	0 to 48 weeks, N = 544
	LUM/IVA, n (%)
Elevated transaminases	[redacted]
Alanine aminotransferase, increased	[redacted]
Aspartate aminotransferase, increased	[redacted]
Hepatic enzyme, increased	[redacted]
Liver function test, abnormal	[redacted]
Transaminases, increased	[redacted]
Liver-related AEs leading to discontinuation	[redacted]
Serious liver-related AEs	[redacted]

AE = adverse event; LUM/IVA = 400 mg lumacaftor q12h + 250 mg ivacaftor q12h; q12h = every 12 hours.
Note: Data are cumulative and include AEs from TRAFFIC and TRANSPORT as well as PROGRESS.

TABLE 34: RESPIRATORY ADVERSE EVENTS CUMULATIVE TO WEEK 48

Respiratory AEs, n (%)	0 to 48 weeks, N = 544
	LUM/IVA
Respiratory symptoms	
Any AESI of respiratory symptoms	[redacted]
Chest discomfort	[redacted]
Dyspnea	[redacted]
Respiration, abnormal	[redacted]
Leading to discontinuation	[redacted]
Serious respiratory-related AEs	[redacted]
Reactive airways	
Any AE of reactive airways	[redacted]
Asthma	[redacted]
Bronchial hyperreactivity	[redacted]
Bronchospasm	[redacted]
Wheezing	[redacted]
Leading to discontinuation	[redacted]
Serious airway-related AEs	[redacted]

AE = adverse event; AESI = adverse event of special interest; LUM/IVA = 400 mg lumacaftor q12h + 250 mg ivacaftor q12h; q12h = every 12 hours.
Source: Clinical Study Report for PROGRESS.[64]

Efficacy

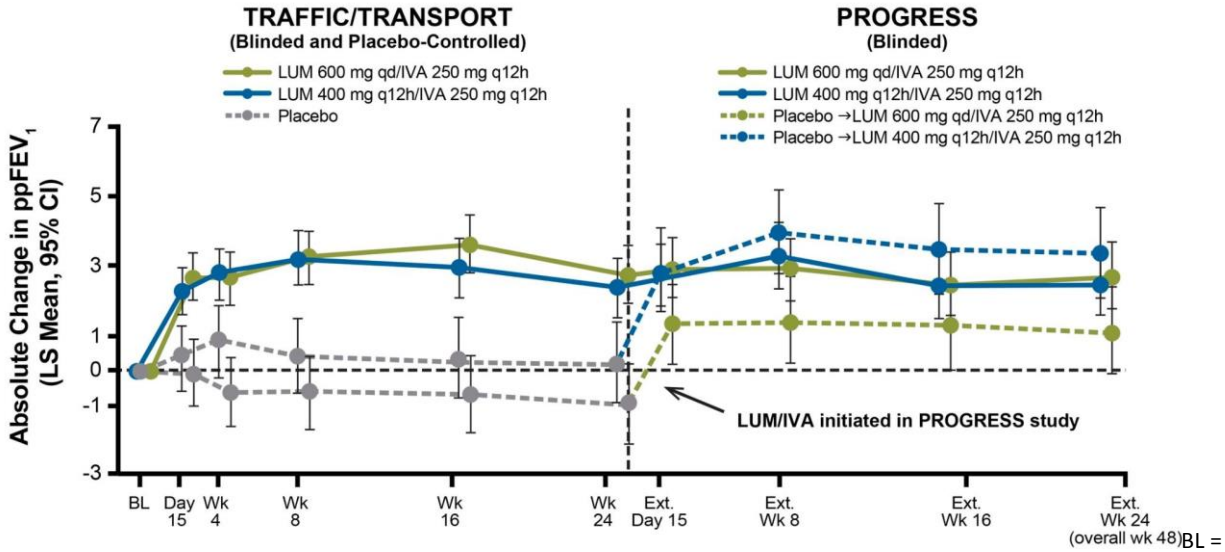
The data detailed in Figure 11 represent the efficacy of LUM in combination with IVA with respect to $ppFEV_1$. The results suggest that the changes from baseline observed in TRAFFIC and TRANSPORT for those who took LUM/IVA were sustained up to week 24 of PROGRESS. The results also suggest similar efficacy in $ppFEV_1$ upon receiving LUM/IVA for those who received placebo in TRAFFIC and TRANSPORT. The data detailed in Figure 12 represent the absolute change from baseline in BMI. For those taking LUM/IVA in TRAFFIC and TRANSPORT, the data suggest continued improvement throughout the PROGRESS study, albeit a considerably more subtle improvement. The results also suggest improvement in BMI upon receiving LUM/IVA for those who were receiving placebo in TRAFFIC and TRANSPORT.

Pulmonary exacerbation data are reported in Table 12. The results suggest that the rates of pulmonary exacerbations, pulmonary exacerbations requiring hospitalization, and pulmonary exacerbations requiring IV antibiotic therapy up to 24 weeks of PROGRESS were similar to those observed in TRAFFIC and TRANSPORT. Similar results were observed for patients who were treated with placebo in the pivotal studies and crossed over to LUM/IVA in PROGRESS. In terms of time to first pulmonary exacerbation, the results suggest that the benefits experienced by those on active treatment at week 24 in TRAFFIC and TRANSPORT were similar to the benefit observed at week 24 for those on active treatment in PROGRESS and assigned placebo in the previous studies. With respect to the proportion of patients experiencing at least one pulmonary exacerbation, the results suggest improvement between those on active treatment at week 24 in PROGRESS and those on placebo at week 24 in the pivotal studies. The observed benefit is similar to that seen in the LUM/IVA group at week 24 of the pivotal studies.

The data detailed in Figure 13 represent the absolute change from baseline in the CFQ-R–respiratory domain score. The results suggest that the benefits observed in TRAFFIC and TRANSPORT for those who

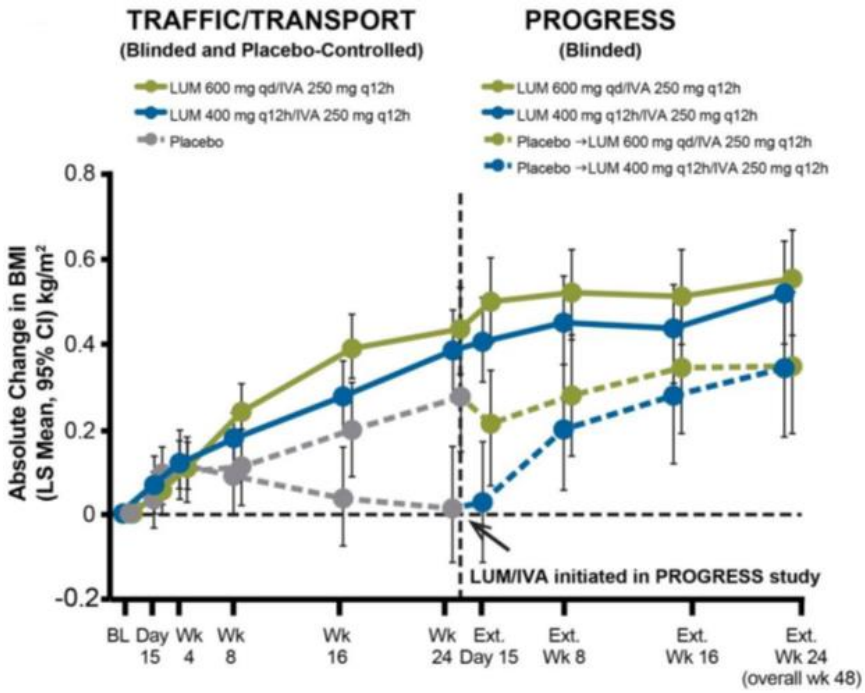
took LUM/IVA are sustained up to week 24 of PROGRESS. The results also suggest similar benefits upon receiving LUM/IVA for those who were taking placebo in the previous studies.

FIGURE 11: ABSOLUTE CHANGE FROM BASELINE IN ppFEV$_1$ (FULL ANALYSIS SET)



BL = baseline; ext. = extension phase; CI = confidence interval; LS = least squares; LUM/IVA = lumacaftor and ivacaftor; ppFEV$_1$= per cent predicted forced expiratory volume in 1 second; qd = once daily; q12h = every 12 hours; wk = week.
Source: Reproduced from Konstan et al., 2015.[75]

FIGURE 12: ABSOLUTE CHANGE FROM BASELINE IN BODY MASS INDEX (FULL ANALYSIS SET)



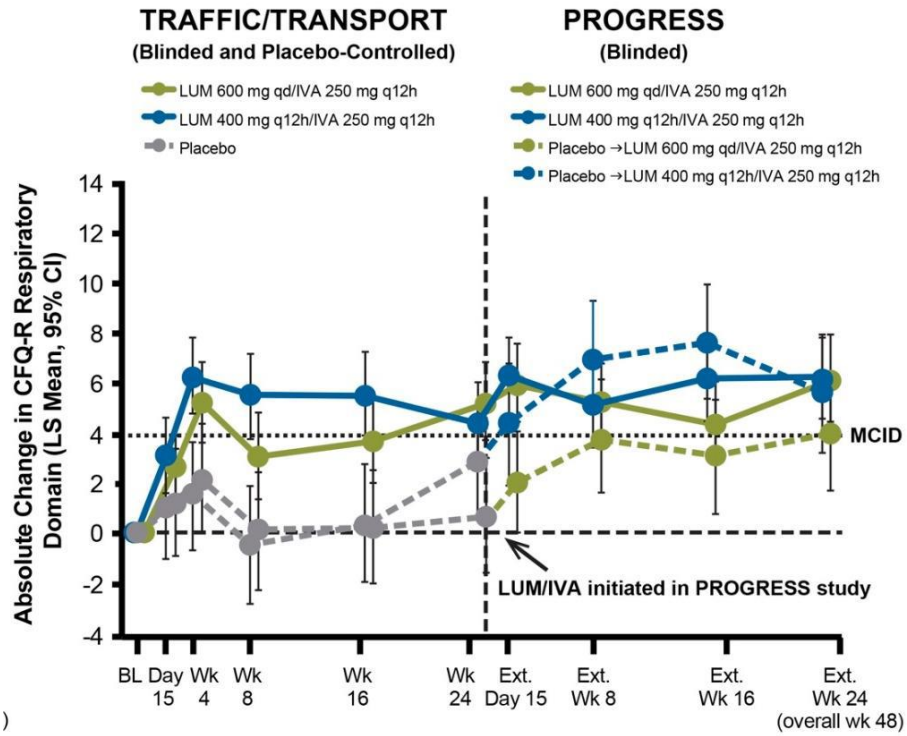
BL = baseline; BMI = body mass index; CI = confidence interval; ext. = extension phase; FAS = full analysis set; LS = least squares; LUM/IVA = lumacaftor and ivacaftor; q12h = every 12 hours; qd = once daily; wk = week.
Source: Reproduced from Konstan et al., 2015.[75]

TABLE 35: PULMONARY EXACERBATIONS THROUGH WEEK 24 OF PROGRESS (FULL ANALYSIS SET)

End Points	Planned Treatment		Placebo From TRAFFIC/ TRANSPORT[a] (N = 355)
	LUM/IVA (N = 340)	Pbo then LUM/IVA (N = 176)	
Pulmonary exacerbations			
Event rate per year (95% CI)	[redacted]	[redacted]	[redacted]
Time to first pulmonary exacerbation			
Exacerbation-free probabilities	[redacted]	[redacted]	[redacted]
Pulmonary exacerbations requiring hospitalization			
Event rate per year (95% CI)	[redacted]	[redacted]	[redacted]
Pulmonary exacerbations requiring IV antibiotic therapy			
Event rate per year (95% CI)	[redacted]	[redacted]	[redacted]
At least one pulmonary exacerbation			
Patients with event, n (%)	[redacted]	[redacted]	[redacted]

CI = confidence interval; IV = intravenous; LUM/IVA = 400 mg lumacaftor q12h + 250 mg ivacaftor q12h;
Pbo then LUM/IVA = placebo in pivotal studies and 400 mg lumacaftor q12h + 250 mg ivacaftor q12h in PROGRESS;
q12h = every 12 hours.
[a] Placebo results at week 24 from TRAFFIC and TRANSPORT.
[b] Exacerbation-free probabilities at week 24 for those on active treatment in TRAFFIC and TRANSPORT.
[c] Proportion of patients suffering at least one pulmonary exacerbation after 48 weeks of active treatment (24 weeks in TRAFFIC and TRANSPORT and 24 weeks in PROGRESS).
Source: Clinical Study Report for PROGRESS.[64]

FIGURE 13: ABSOLUTE CHANGE FROM BASELINE IN CFQ-R–RESPIRATORY DOMAIN SCORE (FULL ANALYSIS SET)



BL = baseline; CI = confidence interval; ext. = extension phase; CFQ-R = Cystic Fibrosis Questionnaire–Revised; CI = confidence interval; FAS = full analysis set; LS = least squares; LUM/IVA = lumacaftor and ivacaftor; MCID = minimal clinically important difference; qd = once daily; q12h = every 12 hours; wk = week.
Source: Reproduced from Konstan et al., 2015.[75]

Limitations

There are many important limitations related to PROGRESS, the main ones being that it was an interim analysis of an ongoing trial with no control group. Without a control group, it is difficult to assess the long-term efficacy and safety. It remains uncertain whether the changes observed in the clinical outcomes were due to a natural course of the disease or were attributed to long-term treatment with LUM/IVA. In addition, it should be noted that the baseline characteristics at the end of TRAFFIC and TRANSPORT for those on placebo were not presented in PROGRESS. It remains unclear if the baselines at the end of TRAFFIC and TRANSPORT or the baselines at the start of TRAFFIC and TRANSPORT were utilized in making the efficacy and safety assessments in PROGRESS for those taking placebo in the previous studies, thereby making it difficult to make concrete assessments of the effects and harms attributed to long-term treatment with LUM/IVA. There is potential for an overestimation of the efficacy and underestimation of the adverse events due to the fact that the patients who discontinued either may not have been able to tolerate or may not have responded on LUM/IVA, leaving only those able to tolerate and benefit long-term. Also, the safety analyses pooled the patients who were on LUM/IVA in the previous studies with the patients who were on placebo and switched to LUM/IVA in PROGRESS. This makes it difficult to truly determine the safety concerns caused by the active treatment or caused by a carry-over effect from the previous studies.

2. Summary

In general, the ongoing PROGRESS study suggests that improvements in all reported outcomes persisted and were similar to those observed in the pivotal studies after 48 weeks of treatment. Overall, treatment with LUM/IVA was generally well tolerated and raised no new safety concerns. However, caution is required when interpreting the results of this study, given the high degree of uncertainty resulting from the key limitations.

APPENDIX 7: SUMMARY OF F508DEL MUTATION TESTING

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To summarize the use of F508del mutation testing in patients with cystic fibrosis (CF).

Findings

Description of F508del Mutation

F508del is the most common mutation that results in CF and is characterized as a class II defect.[76] Class II defects are among those associated with more severe manifestations of CF, resulting in complete loss of chloride channel function.[76] The cystic fibrosis transmembrane conductance regulator (CFTR) gene with the F508del mutation presents a deletion of three base pairs, involving the loss of an amino acid, phenylalanine, at position 508.[76] This results in a three-fold problem leading to loss of chloride channel function. The first is a defect in the spatial conformation; when the protein reaches the endoplasmic reticulum, the cell's quality control mechanism recognizes the protein as "misfolded" and degrades it soon after synthesis, before reaching the cell surface.[76] Secondly, when allowed to traffic out of the endoplasmic reticulum (e.g., by overexpression), the CFTR with the F508del mutation has a reduced half-life compared with that of normal CFTR.[76] The third problem is associated with gating. Chloride channel gating of the CFTR protein with the F508del mutation is defective such that its open probability is reduced by more than three times that compared with that of normal CFTR protein.[76] According to the Canadian Cystic Fibrosis Registry, 50.0% of the 3,972 CF patients in the registry were homozygous for F508del mutations and 89.7% of patients had at least one F508del mutation.[3]

Description of F508del Mutation Testing

Deoxyribonucleic acid (DNA) sequencing is considered the "gold standard" for DNA-based mutation testing.[77] However, for clinical laboratory settings, routine DNA sequencing is currently not practical or cost-effective in most centres for identifying CFTR gene mutations, with more than 1,800 reported mutations in the CF gene.[78,79] Hence, the American College of Medical Genetics (ACMG) and the American College of Obstetrics and Gynecology (ACOG) recommend testing patients diagnosed with, or at risk for, CF for the 23 most common CF mutations (including the F508del mutation), representing mutations with an allele frequency of ≥ 0.1% in the general population.[77,80] The new ACMG panel of 23 mutations accounts for 94.04% of detectable mutations.[77] Several CFTR mutation testing systems have been developed to detect the most frequently occurring CF gene mutations. These systems use multiplex polymerase chain reaction (PCR)-based hybridization (with mutation-specific oligonucleotide probes) to detect the ACMG/ACOG 23 mutations. Some testing systems test for extra mutations beyond the minimum 23 that may be of clinical interest;[78] one panel included 106 mutations, which account for approximately 91% of CF genes in a Northern European Caucasian population.[81]

Various procedures for molecular diagnosis of CF are reported in the literature, including allele-specific oligonucleotide dot-blot , reverse dot-blot , amplification refractory mutation system (ARMS), and oligonucleotide ligation assay (OLA) PCR.[82] Commercially available CF testing platforms include the eSensor CF carrier detection system, CF v3.0 OLA analyte-specific reagent (ASR), CFTR InPlex ASR, Signature CF 2.0 ASR, INNO-LiPA CFTR 35, CF Gold 1.0, Tag-It CF 40 + 4, CF eMAP/Bead Chip, and Invader.[82] Among the above-mentioned platforms, only Tag-It CF 40 + 4 is used in Canada (Tm Biosciences, Toronto, Ontario, Canada).[82] In one study,[82] Johnson et al. evaluated five CFTR testing platforms: the eSensor CF carrier detection system CFTR, InPlex ASR; CF v3.0 OLA ASR; Signature CF 2.0

ASR; and Tag-It mutation detection kit for CFTR 40 + 4. The authors subjected each platform to seven independent amplifications and runs with the same core set of 150 DNA samples (representing the ACMG/ACOG-recommended panel of 23 CFTR mutations and normal samples) to assess the performance of each platform. Of the panels evaluated, InPlex tested for the greatest number of mutations (42 in total). All platforms demonstrated good specificity and sensitivity (100% concordance) and acceptable test repeat rates (all ≤ 0.7%). The start-to-finish time and hands-on time were similar across all platforms, although the InPlex system required the least time in both categories. Likewise, all were considered relatively easy to use (based on number of steps, tolerances within those steps, and number of sample transfers) and again the InPlex system was considered the better platform. All of the platforms require specialized instrumentation. With the exception of the eSensor, additional tests can be run using the same instrumentation. In addition, three platforms — Tag-It, Signature, and OLA — are open platforms and allow development of custom tests. It is perhaps not surprising that there were few differences in performance between the platforms evaluated by Johnson et al.,[82] since the manufacturers likely follow the ACMG/ACOG standards and guidelines for CFTR tests, which specify the type of test that should be used (i.e., PCR-based) and criteria for the analytical and clinical validity of tests.[77]

Current Canadian Practice Regarding F508del Testing

The Canadian College of Medical Geneticists (CCMG) committee endorsed CFTR mutation testing for use in individuals or families at increased risk of CF due to family history considerations or clinical manifestations.[83] The clinical expert consulted for this review confirmed that F508del mutation testing is part of the standard panel of mutations used in screening CF patients. However, in terms of testing systems or platforms, no specific F508del-CFTR mutation testing recommendation was identified in the CCMG guideline (2011).[83] The limited search of the published and grey literature for this review revealed that the Tag-It CF 40 + 4 platform is used in Canada, but there was very little publicly available information on many aspects of CF mutation testing in Canada, including what tests are used, their performance, and issues concerning access, availability, and the cost of the tests. According to CF Canada, 97% of Canadian CF patients have had genotyping performed.[3]

Conclusion

DNA sequencing is the gold standard for CFTR mutation testing; however, it is not practical or cost-effective in routine clinical practice. The ACMG/ACOG recommendation is to test for the 23 most common mutations, including the F508del mutation, in people with, or at risk for, CF. All CFTR mutation tests use multiplex PCR as the DNA assay method. In terms of CFTR mutation testing systems or platforms, no recommendation was identified in the CCMG guideline (2011). Based on the limited literature search for this review, Tag-It CF 40 + 4 is the only platform used in Canada. There was very little published or publicly available information on many aspects of the CF mutation tests used in Canada, including confirmation of what tests are used, their performance, and issues concerning access, availability, and the cost of the tests.

APPENDIX 8: SUMMARY OF THE ROLE OF SWEAT CHLORIDE TESTING IN CF

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To summarize the role of sweat chloride testing in cystic fibrosis (CF).

Findings

Guidelines developed by the Cystic Fibrosis Foundation indicate that a combination of clinical presentation, laboratory testing, and genetic testing is required to confirm a diagnosis of CF.[84] The Canadian College of Medical Geneticists recommends that all provincial newborn screening programs should offer screening for CF; immunoreactive trypsinogen on a newborn blood spot is considered the first-line test.[85] Newborns with a positive screening result, or older children with clinical signs or symptoms, should be referred for further diagnostic testing. The sweat chloride test is considered the gold standard for CF diagnosis.[84] See Table 36 below for Cystic Fibrosis Foundation recommendations related to interpretation of sweat chloride testing.

TABLE 36: RECOMMENDED SWEAT CHLORIDE REFERENCE VALUES IN THE DIAGNOSIS OF CYSTIC FIBROSIS

Age at Testing	Interpretation of Sweat Chloride Test Results
Infancy (up to 6 months of age)	• ≤ 29 mmol/L, CF unlikely • 30 mmol/L to 59 mmol/L, intermediate • ≥ 60 mmol/L, indicative of CF Individuals with intermediate results should undergo repeat sweat chloride testing and then be referred to a CF centre with expertise in diagnosing CF in infancy. Further evaluation should include early detailed clinical assessment, more extensive CFTR gene mutation analysis, and repeat sweat chloride testing and follow up at 6- to 12-month intervals until diagnosis is clear.
Beyond infancy (> 6 months of age)	• ≤ 39 mmol/L, CF unlikely • 40 mmol/L to 59 mmol/L, intermediate • ≥ 60 mmol/L, indicative of CF Individuals with intermediate results should undergo repeat sweat chloride testing and further evaluation, including detailed clinical assessment and more extensive CFTR gene mutation analysis. Clinical follow-up should occur at 6- to 12-month intervals, and repeat sweat chloride testing should be performed periodically, particularly if a change in symptoms occurs, until the diagnosis is clear.

CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator.
Source: Farrell et al.[84]

Researchers have proposed that sweat chloride concentrations could be a potential outcome measure in the study of drugs targeting CFTR gene dysfunction;[86,87] however, it does not appear that drug-associated changes in sweat glands (resulting in a reduction in sweat chloride levels) correlate with changes in respiratory function.[86,87]

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