CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

LUMACAFTOR/IVACAFTOR (ORKAMBI)

(Vertex Pharmaceuticals (Canada) Incorporated)

Indication: For the treatment of cystic fibrosis in patients aged six years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene.

Service Line:	CADTH Common Drug Review
Version:	Final (with redactions)
Publication Date:	October 2018
Report Length:	184 Pages

CADTH

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Table of Contents

Abbreviations 7
Executive Summary 8
Introduction 8
Results and Interpretation 8
Conclusions 15
Introduction 22
Disease Prevalence and Incidence 22
Standards of Therapy 23
Drug 23
Objectives and Methods 26
Objectives 26
Methods 26
Results 29
Findings from the Literature 29
Included Studies 33
Patient Disposition 51
Exposure to Study Treatments 53
Critical Appraisal 56
Efficacy 64
Harms 79
Discussion 92
Summary of Available Evidence 92
Interpretation of Results 93
Conclusions 104
Appendix 1: Patient Input Summary 106
Appendix 2: Literature Search Strategy 109
Appendix 3: Detailed Outcome Data 112
Appendix 4: Description and Appraisal of Outcome Measures 123
Appendix 5: Summary of Study 106 (Advanced Lung Disease) 130
Appendix 6: Summary of PROGRESS and Registry Analysis 139
Appendix 7: Summary of Extension Study 110 169
Appendix 8: Summary of F508del Mutation Testing 175
References 178

Tables

Table 1: Summary of Key Efficacy Results for Patients Aged 12 Years and Older 17
Table 2: Summary of Key Efficacy Results for Patients Aged Six Years to 11 Years 20
Table 3: Summary of Adverse Events 21
Table 4: Indication and Requested Listing Criteria 24
Table 5: Recommended Dosage Adjustment for Hepatic Impairment 24
Table 6: Inclusion Criteria for the Systematic Review 26
Table 7: Details of Included Studies for Patients 12 Years and Older 30
Table 8: Details of Included Studies for Patients Six Years to 11 Years 32
Table 9: Summary of Studies 34
Table 10: Summary of Demographic and Baseline Characteristics 38
Table 11: Summary of Demographic and Baseline Characteristics for Patients Six Years to 11 Years 39
Table 12: Summary of Study Drug Administration in TRANSPORT and TRAFFIC 40
Table 13: Key Efficacy End Points 41
Table 14: Statistical Analysis of Efficacy End points 47
Table 15: Analysis Sets 50
Table 16: Patient Disposition 52
Table 17: Summary of Exposure to Study Drugs 54
Table 18: Prior Use of Medications for Cystic Fibrosis Medications 55
Table 19: Change from Baseline in Lung Clearance Index from Study 109 69
Table 20: Time-to-First Pulmonary Exacerbation in TRAFFIC and TRANSPORT 71
Table 21: Absolute Changes from Baseline in BMI, Weight, and Height at week 24 from TRAFFIC, TRANSPORT, Study 112, and Study 109 75
Table 22: Absolute Change from Baseline in Z Scores for BMI, Weight, and Height at Week 24 from TRAFFIC, TRANSPORT, and Study 109 77
Table 23: Absolute Change from Baseline in CFQ-R Respiratory Domain and EQ-5D-3L from TRAFFIC, TRANSPORT, Study 112, and Study 109 79
Table 24: Summary of Adverse Events 80
Table 25: Adverse Events Reported for at Least Five Per Cent of Patients 82
Table 26: Serious Adverse Events 84
Table 27: Withdrawals Due to Adverse Events 85
Table 28: Hepatic Adverse Events 87
Table 29: Respiratory Adverse Events 89
Table 30: Timing of Onset and Duration of Respiratory Adverse Events 90
Table 31: Timing of Onset and Duration of Respiratory Adverse Events 91
Table 32: Change in $ppFEV_1$ at Each Study Visit in TRAFFIC and TRANSPORT 112
Table 33: Subgroup Analyses for $ppFEV_1$ in TRAFFIC and TRANSPORT 113

Table 34: Sensitivity Analyses for $ppFEV_1$ from TRAFFIC and TRANSPORT 115
Table 35: Subgroup Analyses for Absolute Change from Baseline in $LCI_{2.5}$ 115
Table 36: Subgroup Analyses for Pulmonary Exacerbations from TRAFFIC and TRANSPORT .. 116
Table 37: Change in CFQ-R (RD) at Each Study Visit in TRAFFIC and TRANSPORT 116
Table 38: Change in CFQ-R (RD) at Each Study Visit in Study 109 117
Table 39: Change in CFQ-R (RD) at Each Study Visit in Study 109 119
Table 40: Changes in BMI, Weight, and Height from Study 11B 120
Table 41: Summary of Adverse Events from TRAFFIC and TRANSPORT 121
Table 42: Respiratory Adverse Events by FEV_1 at Baseline (A) or Screening (B) 122
Table 43: Summary of Appraisal of Outcome Measures 123
Table 44: Inter-Test Reproducibility of the Lung Clearance Index in Preschool Children 126
Table 45: Patient Disposition in Study 106 131
Table 46: Baseline Characteristics in Study 106 132
Table 47: Adverse Events from Study 106 133
Table 48: Summary of Efficacy Outcomes in Study 106 133
Table 49: Patient Disposition in PROGRESS 143
Table 50: Baseline Characteristics in PROGRESS 144
Table 51: Exposure to Lumacaftor/Ivacaftor in PROGRESS 145
Table 52: Pulmonary Exacerbations in PROGRESS 146
Table 53: Absolute Change in $ppFEV_1$ in PROGRESS 147
Table 54: Absolute Change in BMI and BMI Z Score in PROGRESS 150
Table 55: Absolute Change in CFQ-R Respiratory Domain Score From PROGRESS 152
Table 56: Summary of Adverse Events in PROGRESS 154
Table 57 : Summary of Adverse Events Cumulative to Week 120 in PROGRESS 155
Table 58: Risk Factors Included in Propensity Score Logistic Regression Model 157
Table 59: Effect Sizes for Binary Variables Used for Propensity Score Matching — Registry Comparator Analysis 159
Table 60: Effect Sizes for Binary Variables Used for Propensity Score Matching — Registry Comparator Analysis 160
Table 61: Baseline Characteristics in Registry Comparator Analysis 161
Table 62: Summary of Results from Registry Comparator Analysis 161
Table 63: Sensitivity Analyses for Annualized Rate of Change in $ppFEV_1$ from Registry Comparator Analysis 162
Table 64: Exposure to Lumicaftor/Ivacaftor During Study 110 170
Table 65: Baseline Patient Characteristics from Study 110 171
Table 66: Adverse Events from Study 110 172

Figures

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies 29
Figure 2: Schematic Showing Design of Studies in Patients 12 Years and Older (A) and Six Years to 11 Years (B) 36
Figure 3: Absolute and Relative Change in $ppFEV_1$ from TRAFFIC, TRANSPORT, Study 112, and Study 109 65
Figure 4: Absolute and Relative Change in $ppFEV_1$ from TRAFFIC, TRANSPORT, and Study 109 66
Figure 5: Subgroup Analyses for Absolute Change in $ppFEV_1$ in TRAFFIC and TRANSPORT 67
Figure 6: Responder Analysis of Average Change from Baseline in $ppFEV_1$ From TRAFFIC and TRANSPORT 68
Figure 7: Absolute change from baseline in $LCI_{2.5}$ in Study 109 69
Figure 8: Risk of Pulmonary Exacerbations from TRAFFIC, TRANSPORT, and Study 109 72
Figure 9: Change from Baseline in Body Mass Index from TRAFFIC, TRANSPORT, Study 112, and Study 109 73
Figure 10: Change from Baseline in Z Scores for Body Mass Index, Body Weight, and Height from TRAFFIC, TRANSPORT, and Study 109 74
Figure 11: Absolute Change from Baseline in $ppFEV_1$ in Study 106 135
Figure 12: Absolute Change from Baseline in CFQ-R Respiratory Domain in Study 106 136
Figure 13: Absolute Change from Baseline in BMI from Study 106 137
Figure 14: Design of the PROGRESS Extension Study 140
Figure 15: Time-to-first pulmonary exacerbation in PROGRESS 146
Figure 16: Absolute and Relative Change From Baseline in $ppFEV_1$ in PROGRESS 148
Figure 17: Responder Analysis for $ppFEV_1$ in PROGRESS 149
Figure 18: Absolute Change from Baseline in BMI (A) and BMI Z Score (B) from PROGRESS 151
Figure 19: Absolute Change From Baseline in CFQ-R Respiratory Domain Score in PROGRESS 153
Figure 20: Annual Rate of Change in $ppFEV_1$ — Registry Comparator Analysis 163
Figure 21: Annual Rate of Change in Weight-For-Age Z Score (A), BMI Z Score (B), and BMI (C) — Registry Comparator Analysis 164
Figure 22: Schematic of Extension Study 110 169
Figure 23: Absolute Change from Baseline in $ppFEV_1$ for Studies 11B and 110 173
Figure 24: Absolute Change from Baseline in BMI Z Score for Studies 11B and 110 174

Abbreviations

ANCOVA	analysis of covariance
AE	adverse event
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 3-Levels questionnaire
FAS	full analysis set
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
IV	intravenous
IVA	ivacaftor
IWRS	interactive Web response system
MCID	minimal clinically important difference
MMRM	mixed-effects model for repeated measures
NICE	National Institute for Health and Care Excellence
LCI	lung clearance index
LSMD	least squares mean difference
L200/IVA	LUM 200 mg every 12 hours/IVA 250 mg every 12 hours
L400/IVA	LUM 400 mg every 12 hours/IVA 250 mg every 12 hours
LUM	lumacaftor
LUM/IVA	lumacaftor/ivacaftor
PBAC	Pharmaceutical Benefits Advisory Committee
$ppFEV_1$	per cent predicted forced expiratory volume in one second
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SMC	Scottish Medicines Consortium
VAS	visual analogue scale
$VO2_{max}$	maximal oxygen consumption
WDAE	withdrawals due to adverse event

Drug	lumacaftor/ivacaftor (Orkambi)
Indication	For the treatment of cystic fibrosis in patients aged six years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene
Reimbursement Request	As per indication
Dosage Form	lumacaftor 200 mg/ivacaftor 125 mg tablets
NOC Date	April 18, 2017
Manufacturer	Vertex Pharmaceuticals (Canada) Incorporated

Executive Summary

Introduction

Orkambi is a fixed-dose combination tablet containing lumacaftor and ivacaftor (LUM/IVA). It is indicated for the treatment of cystic fibrosis (CF) in patients aged six years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane regulator (CFTR) gene. This is the most common CF-causing mutation worldwide and approximately half of all Canadian patients with CF are homozygous for the F508del mutation. 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 reimburse in accordance with the Health Canada–approved indication.

CADTH previously reviewed LUM/IVA for treatment of patients aged 12 years and older. The indication was subsequently expanded to include patients who are least six years of age. The current CADTH Common Drug Review submission is for the full Health Canada–approved indication.

Results and Interpretation

Included Studies

The CADTH systematic review included four double-blind (DB), placebo-controlled, randomized controlled trials (RCTs) (TRAFFIC, TRANSPORT, Study 112, and Study 109) and one pivotal, single-arm, open-label trial (Study 11B). In addition, the CADTH review included the following studies as supplemental information: two extension phase studies (PROGRESS and Study 110) and a single-arm study conducted in patients with severe lung disease (Study 106). The study populations consisted of patients who were either six years to 11 years of age (studies 109, 110, and 11B) or patients who were at least 12 years of age (TRAFFIC, TRANSPORT, PROGRESS, Study 106, and Study 112). All of the studies included a screening phase (up to 28 days), an investigational treatment period (24 weeks), and a safety follow-up phase (approximately four weeks). The use of placebo as

the comparator in the RCTs is appropriate as LUM/IVA is currently the only treatment approved in Canada for use in the treatment of CF in patients with F508del-CFTR mutations. All of the studies compared the addition of LUM/IVA (or placebo) with ongoing standard CF-management therapies, which is reflective of how LUM/IVA would be administered in routine clinical practice.

Patients Aged 12 and Older

TRAFFIC (N = 559) and TRANSPORT (N = 563) were the pivotal studies for patients 12 years and older. These were identically designed phase III, randomized, DB, placebo-controlled studies conducted to evaluate the efficacy and safety of LUM/IVA in patients with CF homozygous for the F508del-CFTR mutation who were aged 12 years and older. The CADTH 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 [L400/IVA]). Both TRAFFIC and TRANSPORT also included an additional LUM/IVA dosage regimen (LUM 600 mg daily/IVA 250 mg every 12 hours), which was excluded from the CADTH review as it is not currently recommended in the product monograph and could not be achieved using the formulations of LUM/IVA that are marketed in Canada (i.e., tablets containing 100 mg or 200 mg of LUM and 125 mg of ivacaftor). Study 112 (N = 70) was a small phase 4, randomized, placebo-controlled study conducted to evaluate the effect of L400/IVA on manifestations of CF affected by exercise tolerance and training.

Patients aged 12 years and older were eligible for inclusion in TRAFFIC, TRANSPORT, or Study 112 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 or nutritional abnormalities. Patients were also required to have stable CF disease in the opinion of the investigator, and a per cent predicted forced expiratory volume in one second ($ppFEV_1$) of ≥ 40% and ≤ 90% at the time of screening.

Patients Aged Six Years to 11 Years

Both Study 11B and Study 106 were conducted to evaluate the safety and efficacy of LUM/IVA in patients with CF between the ages of six years and 11 years of age who are homozygous for the F508del-CFTR mutation. Study 11 was a pivotal, open-label, two-part, single-arm study. Part A was a 14-day phase I study used to select the dosage for use in Part B, a 24-week phase III study. In accordance with the systematic review protocol, this review has focused only on Part B of the study (i.e., Study 11B). Study 109 was a DB, phase III, placebo-controlled RCT where eligible patients were randomized (1:1) to receive LUM 200 mg/IVA 250 mg every 12 hours (L200/IVA) or placebo. Patients between six years and 11 years of age were eligible for inclusion in studies 11B and 109 if they were homozygous for the F508del-CFTR mutation, had a diagnosis of CF with F508del-CFTR mutation on both alleles, and either chronic sinopulmonary disease or gastrointestinal or nutritional abnormalities, stable disease in the opinion of the study investigator, and ppFEV1 ≥ 40% and ≤ 90% (Study 11B) or ≥ 70% and ≤ 90% (Study 109).

Efficacy

Patients Aged 12 and Older

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. Potential improvements in lung function can be evaluated based on short-term changes from baseline (e.g., absolute or relative change from baseline in $ppFEV_1$ or lung clearance index [LCI] 2.5% as measured in the clinical trials) or long-term changes evaluating the impact of an intervention on the course of CF (e.g., slope of decline as modelled in PROGRESS and the matched cohort study). When considering lung function measurements in a chronic condition such as CF, the ability of a treatment such as LUM/IVA to result in longer-term changes are generally considered by regulatory authorities, health technology assessment agencies, and clinical experts to be more clinically relevant than acute changes in $ppFEV_1$. In this review of LUM/IVA, the manufacturer has submitted both short-term and long-term analyses of $ppFEV_1$.

With respect to the data from the short-term studies (i.e., 24 weeks), L400/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 with L400/IVA was relatively consistent across all of the subgroups that were studied in TRAFFIC and TRANSPORT; however, there were wide confidence intervals (CI) in some subgroup analyses due to the small number of patients (e.g., $ppFEV_1 < 40\%$ or aged 12 years to 18 years). Placebo-treated patients who were crossed over to L400/IVA in the PROGRESS study also demonstrated an increase from baseline in $ppFEV_1$ at 24 weeks (3.4%). The clinical experts consulted for this review indicated that a short-term change in $ppFEV_1$ of the magnitude observed in the TRAFFIC and TRANSPORT studies was modest and of uncertain clinical benefit. While no published information on the minimal clinically important difference for absolute change in $ppFEV_1$ in CF was identified by CADTH, the clinical experts consulted by CADTH noted that specialists in CF would generally consider an absolute improvement in $ppFEV_1$ of at least 5% to be clinically significant. In a responder analysis, 26.8% of L400/IVA-treated patients in the TRAFFIC and TRANSPORT studies achieved an absolute increase of at least 5% in $ppFEV_1$ compared with 14.0% in the placebo group (odds ratio: 2.26 [95% CI, 1.55 to 3.29]). Although the magnitude of improvement in the short-term analyses is modest, reviewers for Health Canada, the European Medicines Agency, and the US Food and Drug Administration concluded that, since FEV_1 is correlated with mortality, the observed improvement in FEV_1 may be clinically relevant for patients with F508del mutations.

The ability of an intervention to result in long-term changes in lung function is a more accurate reflection of CF treatment goals and is considered to be a more clinically relevant end point than acute changes in $ppFEV_1$. The initial CADTH review of L400/IVA considered the 24-week data from the first interim analysis of the PROGRESS extension study, which suggested that patients treated with L400/IVA maintained the effects that were observed in the DB phases of TRAFFIC and TRANSPORT (absolute improvement of 2.5% from baseline; $P < 0.0001$). Since the initial CADTH review, the manufacturer has provided additional long-term follow-up data for L400/IVA (i.e., final 96-week data from PROGRESS). The absolute improvement in $ppFEV_1$ was gradually reduced throughout the PROGRESS study, from 2.7% (95% CI, 1.8 to 3.6) at 24 weeks, to 1.4% (95% CI, 0.5 to 2.4) at 48 weeks, and 0.5% (95% CI, –0.4 to 1.5) at 72 weeks.

With respect to evaluating the impact of LUM/IVA on the rate of lung function decline in patients with CF, the manufacturer has conducted a post hoc matched-registry cohort analysis (Appendix 6). This matched-registry cohort analysis compared patients with CF treated with L400/IVA from PROGRESS (N = 455) with patients from the US Cystic Fibrosis Foundation Patient Registry (N = 1,588). The analysis suggested that the slope of decline in lung function (i.e., $ppFEV_1$) was reduced in patients who were treated with L400/IVA compared with a matched cohort of patients from the US registry (–1.33% versus –2.29% per year over a two-year period). CADTH identified a number of important limitations with the cohort analysis that limit the ability to draw conclusions regarding the impact of L400/IVA on the long-term lung function of Canadian patients with CF. The following key issues with the study may have biased the results in favour of L400/IVA: use of registry patients exclusively from the US, as it has been documented that outcomes for patients with CF in the US are worse than Canadian patients with CF; the generation of propensity scores did not include important potential confounders (e.g., pulmonary exacerbation frequency and socioeconomic status); the balance across the full range of patients and important subgroups were not presented, thus whether balance was fully achieved and how this may have affected the study results is uncertain. Overall, due to the limitations regarding the long-term extension data and the matched cohort comparison (i.e., absence of a control group, high rate of discontinuation, and generalizability concerns), there remains uncertainty regarding the long-term impact of treatment with LUM/IVA on the lung function of patients with CF.

In both TRAFFIC and TRANSPORT, treatment with L400/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 L400/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 I error. However, the clinical experts involved in the review indicated that the improvements in pulmonary exacerbations were clinically significant. There is consistent reporting from Health Canada, the European Medicines Agency, the US Food and Drug Administration, and the National Institute for Health and Care Excellence (NICE) that the reduction in pulmonary exacerbations that was observed in the TRAFFIC and TRANSPORT studies is likely to be clinically relevant for patients with CF.

Given that 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 with CF. 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. The difference between L400/IVA and placebo was statistically significant in the pre-planned pooled analysis (0.24 kg/m^2 [95% CI, 0.11 to 0.37]). Neither study demonstrated a statistically significant difference between L400/IVA and placebo for changes in the height of patients with CF who were younger than 20 years of age. Treatment with L400/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 3-Levels questionnaire).

Study 112 was a small study that was not designed or powered to detect differences in the end points of interest for CADTH's review. There was no statistically significant difference between L400/IVA and placebo in Study 112 for absolute change from baseline in $ppFEV_1$ (3.4% [95% CI, –1.2 to 8.1]), relative change from baseline in $ppFEV_1$ (3.5% [95% CI, –3.4 to 10.4]), absolute change from baseline in BMI (0.2 [95% CI, −0.3 to 0.6]), or absolute change from baseline in CFQ-R respiratory domain (5.0 [95% CI, –2.6 to 12.7]).

Study 106 was a prospective, open-label, uncontrolled clinical trial in patients (N = 46) who were 12 years of age or older with CF homozygous for F508del-CFTR mutation and with advanced lung disease (defined as $ppFEV_1$ < 40%). Patients were treated with L400/IVA for up to 24 weeks. The mean change from baseline to week 24 in $ppFEV_1$ was –0.4 (95% CI, –1.9 to 1.1). Three patients (7%) had an absolute increase in $ppFEV_1$ of 5% or greater at week 24. Data for the respiratory domain of the CFQ-R and BMI showed no statistically significant change from baseline over 24 weeks. The mean normalized total duration of intravenous (IV) antibiotics for sinopulmonary signs and symptoms was 11.4 days (standard deviation: 18.2) during the 24-week study period compared with 19.9 days (standard deviation: 25.9) in the 24 weeks prior to the study. During the 24-week study period, 16 patients (35%) were hospitalized (in a total of 23 hospitalizations), for an annual event rate of 1.14 (95% CI, 0.70 to 1.84), which was lower than the annual hospitalization rate in the 24 weeks prior to the study (2.87 [95% CI, 1.74 to 4.74]). No conclusions can be made with regards to the efficacy of L400/IVA in this population given the lack of a concurrent control group, the limited sample size, and the extent of missing data.

Patients Aged Six Years to 11 Years

Treatment with L200/IVA was associated with a statistically significant improvement in $LCI_{2.5}$ (the primary end point) compared with placebo (least squares mean difference [LSMD]: –1.09 [95% CI, –1.43 to –0.75]) and in $LCI_{5.0}$ (LSMD: –0.54 [95% CI, –0.72 to –0.35]). Given the lack of evidence supporting the validity of $LCI_{2.5}$ as a surrogate outcome for clinical end points in CF and its absence of use in Canadian practice, the clinical experts consulted by CADTH suggested that the results were of uncertain clinical relevance.

In study 109, treatment with L200/IVA resulted in improvements compared with placebo for absolute change in $ppFEV_1$ (LSMD: 2.4% [95% CI, 0.4 to 4.4]) and relative change in $ppFEV_1$ (LSMD: 3.2% [95% CI, 0.6 to 5.7]). In Study 11B, there was no statistically significant improvement with L200/IVA for absolute change in $ppFEV_1$ (LSMD: 2.5% [95% CI, –0.2 to 5.2]) or relative change in $ppFEV_1$ (LSMD: 1.5% [95% CI, –1.3 to 4.9]). Unlike the TRAFFIC and TRANSPORT studies, Study 109 did not included a responder analysis based on $ppFEV_1$. Given the small magnitude of the improvement and the short 24-week duration of Study 109, the differences in $ppFEV_1$ are of uncertain clinical significance.

In patients aged six years to 11 years of age, pulmonary exacerbations were only reported as an efficacy end point in Study 109 and not in Study 11B. Exacerbations of CF occurred infrequently in Study 109; though the definition used for pulmonary exacerbation was identical to that used in the TRAFFIC and TRANSPORT studies. The clinical expert consulted by CADTH suggested that the diagnosis and measurement of exacerbations in children is often different compared with older patients. There was no statistically significant difference between the L200/IVA and placebo groups in the rate of pulmonary exacerbations in Study 109 (rate ratio: 1.33 [95% CI, 0.70 to 2.53]). There were no statistical comparisons conducted for time-to-first pulmonary exacerbation, hospitalization for pulmonary exacerbation, and pulmonary exacerbations requiring IV antibiotic therapy in Study 109.

Change from baseline in BMI was a key secondary end point of Study 109 and there were no statistically significant differences between L200/IVA and placebo for absolute change from baseline BMI (LSMD: 0.11 [95% CI, −0.08 to 0.31]) and BMI-for-age z score (LSMD: 0.03 [95% CI, −0.07 to 0.13]). Similarly, there were no statistically significant differences between L200/IVA and placebo for changes from baseline in body weight (LSMD: 0.3 [95% CI, −0.1 to 0.7]), weight-for-age z score (LSMD: 0.04 [95% CI, −0.03 to 0.10]), height (LSMD: 0.3 [95% CI, 0.0 to 0.6]), and height-for-age z score (LSMD: 0.03 [95% CI, −0.01 to 0.08]). The clinical experts consulted by CADTH suggested that a longer duration of follow-up would likely be required to observe whether or not treatment with L200/IVA results in a meaningful improvement in the BMI of pediatric patients with CF.

In Study 109, there was no statistically significant difference between L200/IVA and placebo for change from baseline to week 24 in the CFQ-R respiratory domain for either the patient or the parent and caregiver versions (LSMD: 2.5 [95% CI, −0.1 to 5.1] and 2.6 [95% CI, −1.4 to 6.5], respectively). The clinical experts consulted by CADTH noted that the patients enrolled in Study 109 had relatively normal lung function; therefore, it would be challenging to observe differences between the L200/IVA and the placebo groups using the CFQ-R respiratory domain.

In Study 110 (the open-label extension study in patients aged six years to 11 years) data for the absolute change in $ppFEV_1$ and BMI z score showed similar results during the extension period as in the primary study period of Study 11B; however, these data should be interpreted with consideration given the limitations of the study (e.g., uncontrolled study, small sample size, open-label design, and a large amount of missing data).

Harms

Patients Aged 12 and Older

In TRAFFIC and TRANSPORT, the proportion of patients who experienced at least one serious adverse event (SAE) was greater in the placebo group (28.6%) compared with the L400/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 L400/IVA group (24.1% versus 11.1%, respectively). In Study 112, a greater proportion of L400/IVA-treated patients experienced at least one SAE compared with the placebo group (44.1% versus 25.0%). In contrast with TRAFFIC and TRANSPORT, the proportion of patients with serious pulmonary exacerbations was greater in the L400/IVA group compared with the placebo group (23.5% versus 16.7%; though this was only a difference of two patients).

Withdrawals due to adverse events were more common in the L400IVA group compared with the placebo group in both pivotal studies (4.6% versus 1.6%, respectively); however, over 95% of L400/IVA-treated patients completed the 24-week treatment period. There were no withdrawals due to adverse events reported in Study 112. The proportion of patients with adverse events (AEs) leading to treatment interruption were similar between the L400/IVA and placebo groups in TRAFFIC and TRANSPORT (6.0% versus 6.8%, respectively), but were greater in the L400/IVA group of Study 112 (5.9% versus 0%).

The overall proportions of patients who experienced at least one AE were similar between the placebo groups (95.9%) and the L400/IVA group (95.1%). The most common AEs associated with L400/IVA were respiratory and gastrointestinal. AEs that were reported in 5% or more of patients in the L400/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%).

L400/IVA was associated with an increased incidence of respiratory AEs (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 AEs occurred more frequently in patients with poorer lung function; however, the severity of these events was generally similar regardless of baseline lung function.

In Study 106, the majority of patients experienced an AE during the 24-week study period with infective pulmonary exacerbations (59%), respiration abnormal (57%), cough (46%), and dyspnea (44%) reported most frequently. Eight patients (17%) stopped treatment due to AEs, which included respiration abnormal (three patients) and dyspnea or dyspnea exertional (three patients), and 18 patients (39%) experienced one or more SAEs.

Patients Aged Six Years to 11 Years

The proportion of patients who experienced at least one SAE was 12.6% in the L200/IVA group and 10.9% in the placebo group of Study 109. The most commonly reported SAEs in both the L200/IVA and placebo groups was infective pulmonary exacerbations of CF (7.8% versus 5.0%, respectively). The proportion of patients who experienced at least one SAE was lower in study 11B (6.9%), with serious infective pulmonary exacerbations reported for 3.5% of patients. In Study 109, the proportions of patients who withdrew as a result of AEs were similar in the L200/IVA and placebo groups (2.9% versus 2.0%, respectively). A similar proportion withdrew due to AEs in Study 11B (3.4%). In both studies, these events were primarily attributed to increases in liver enzymes.

The overall proportion of patients who experienced at least one AE was similar between the L200/IVA and placebo groups of Study 109 (95.2% and 97.0%, respectively). Cough was the most frequently reported AE in the studies conducted in patients aged six years to 11 years (44.7% and 46.5% with L200/IVA and placebo in Study 109 and 50.0% in Study 11B). In Study 109, AEs that occurred more frequently in L200/IVA-treated patients than in those that received placebo were productive cough (17.5% versus 5.9%), nasal congestion (16.5% versus 7.9%), oropharyngeal pain (14.6% versus 9.9%), headache (12.6% versus 8.9%), increased sputum (10.7% versus 2.0%), abdominal pain upper (12.6% versus 6.9%), rhinorrhea (9.7% versus 5.0%), and rash (5.8% versus 1.0%). Given that airway clearance is an important goal of day-to-day management of CF, a clinical expert consulted by CADTH suggested that the increase in productive cough, sputum, and nasal congestion could potentially be beneficial for patients and an indication that the treatment is working (i.e., mucus is beginning to clear from airways and sinuses).

Study 110 demonstrated no new safety signals with L200/IVA (total median treatment exposure of 492 days). Infective pulmonary exacerbations were the most commonly reported AE (37%) and SAE (12%). Other commonly reported AEs were cough (37%), nasal congestion (18%), oropharyngeal pain (18%), and pyrexia (16%).

Conclusions

CADTH reviewed the evidence for the full Health Canada–approved indication for LUM/IVA in this CADTH Common Drug Review submission, including patients 12 years and older and those aged six years to 11 years of age who are homozygous for the F508del mutation in the CFTR gene. The CADTH systematic review included four DB, placebo-controlled RCTs (TRAFFIC, TRANSPORT, Study 112, and Study 109) and one pivotal single-arm, open-label trial (Study 11B). In addition, CADTH reviewed two extension phase studies (PROGRESS and Study 110) and a single-arm study conducted in patients with severe lung disease (Study 106).

The TRAFFIC and TRANSPORT studies enrolled patients who were at least 12 years of age and had mild-to-moderate lung disease at the time of screening. Both studies demonstrated that 24 weeks of treatment with L400/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%). The manufacturer conducted a matched-registry cohort analysis that suggested the slope of decline in lung function was reduced in patients who were treated with L400/IVA in the PROGRESS study compared with a matched cohort of patients from a US registry (–1.33% versus –2.29% per year over a two-year period). Because of limitations in the analysis, concerns regarding the comparability of the patients from the clinical trials and those from the registry, and issues regarding the generalizability of US registry patients with Canadian patients with CF, it is uncertain if treatment with L400/IVA would have a similar impact on the rate of lung function decline in Canadian patients.

Compared with placebo, L400/IVA demonstrated clinically meaningful reductions in the number and severity of pulmonary exacerbations in patients 12 years and older, including those that required hospitalization and treatment with IV antibiotics, but no conclusions about the statistical significance of these outcomes could be made in TRAFFIC and TRANSPORT due to failure of the statistical testing hierarchy at a higher-order end point. There was inconsistency in the results for changes in BMI, with statistical significance being demonstrated in only one of the trials (TRANSPORT); however, a pre-planned pooled analysis suggested that treatment with L400/IVA was associated with improvements in BMI, though the magnitude of improvement was of uncertain clinical significance. Treatment with L400/IVA was not associated with statistically significant or clinically relevant improvements in health-related quality of life at 24 weeks. Treatment with L400/IVA demonstrated similar effects on $ppFEV_1$, BMI, and pulmonary exacerbations in patients who received placebo in TRAFFIC and TRANSPORT and transitioned to L400/IVA in the PROGRESS study.

In patients aged six years to 11 years, L200/IVA was associated with a statistically significant improvement in $LCI_{2.5}$ compared with placebo after 24 weeks of treatment (absolute reduction of –1.09). The clinical significance of this finding is uncertain as the minimal clinically important difference has not been established for this end point and it is not currently used in Canadian clinical practice. Treatment with L200/IVA resulted in an improvement in $ppFEV_1$ after 24 weeks of treatment compared with placebo (2.4%); however, the clinical significance of this result is uncertain. Treatment with L200/IVA was not associated with statistically significant improvements in nutritional end points (i.e., BMI, BMI-for-age z score, weight, weight-for-age z score, height, or height-for-age z score), rate of pulmonary exacerbations, or CFQ-R respiratory domain compared with placebo. None of the secondary end points in Study 109 were adjusted for multiplicity.

Both L400/IVA and L200/IVA were generally well-tolerated in the study populations with over 95% of LUM/IVA-treated patients completing the 24-week treatment periods. In patients aged 12 years and older, L400/IVA was associated with an increased frequency of respiratory AEs (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. Patients aged six years to 11 years treated with L200/IVA experienced fewer respiratory AEs compared with older patients, possibly due to have better lung function at baseline.

Table 1: Summary of Key Efficacy Results for Patients Aged 12 Years and Older

	TRAFFIC		TRANSPORT		Pooled	
	Placebo (N = 184)	LUM/IVA (N = 182)	Placebo (N = 187)	LUM/IVA (N = 187)	Placebo (N = 370)	L400/IVA (N = 369)
Absolute change in ppFEV$_1$ (%) at 16 weeks and 24 weeks (average)						
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)[b]	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 weeks and 24 weeks (average)						
n (%)	28 (15.2)	43 (23.6)	24 (12.8)	56 (29.9)	52 (14.0)	99 (26.8)
Odds ratio (95% CI)[c]	1.73 (1.02 to 2.94)		2.93 (1.72 to 5.00)		2.26 (1.55 to 3.29)	
P value	0.0428		< 0.0001		< 0.0001	
Relative change in ppFEV$_1$ (%) at 16 weeks and 24 weeks (average)						
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)[b]	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 weeks and 24 weeks (average)						
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[a]		0.0001[a]		< 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[a]		0.0002[a]		< 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)	
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)	

	TRAFFIC		TRANSPORT		Pooled	
	Placebo (N = 184)	LUM/IVA (N = 182)	Placebo (N = 187)	LUM/IVA (N = 187)	Placebo (N = 370)	L400/IVA (N = 369)
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, 0.37)	
P value	0.1938		0.0001		0.0004	
BMI z score at 24 weeks						
BL; mean (SD)	−0.5897 (0.976)	−0.3645 (0.814)	−0.4997 (0.890)	−0.3330 (0.902)	−0.5499 (0.937)	−0.3489 (0.855)
LSM change (SE)	0.015 (0.049)	0.093 (0.054)	−0.067 (0.047)	0.154 (0.045)	−0.024 (0.034)	0.122 (0.035)
LSMD (95% CI)[b]	0.078 (−0.062 to 0.218)		0.222 (0.096 to 0.347)		0.145 (0.051 to 0.239)	
P value	0.2713		0.0006		0.0025	
Weight (kg) at 24 weeks						
BL; mean (SD)	59.09 (11.720)	60.62 (12.240)	58.46 (13.133)	59.19 (12.049)	58.77 (12.440)	59.90 (12.148)
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)[b]	0.30 (−0.26 to 0.86)		0.95 (0.43 to 1.46)		0.62 (0.24 to 1.00)	
P value	0.2992		0.0003		0.0013	
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)[b]	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)	[redacted]	[redacted]	[redacted]	[redacted]	Not pooled	
LSM change (SE)	0.0006 (0.0074)	0.01 (0.0076)	0.0117 (0.00673)	0.0108 (0.00683)		
LSMD (95% CI)[b]	0.0095 (−0.0109 to 0.0298)		−0.0009 (−0.0192 to 0.0174)			
P value	0.3613		0.9214			

	TRAFFIC		TRANSPORT		Pooled	
	Placebo (N = 184)	LUM/IVA (N = 182)	Placebo (N = 187)	LUM/IVA (N = 187)	Placebo (N = 370)	L400/IVA (N = 369)
EQ-5D-3L (VAS) at 24 weeks						
BL; mean (SD)	75.4 (16.42)	73.7 (17.30)	72.8 (17.36)	71.8 (21.76)	Not pooled	
LSM change (SE)	1.4 (1.03)	2.8 (1.04)	3.3 (1.07)	6.6 (1.08)		
LSMD (95% CI)[b]	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 3-Levels; IV = intravenous; LSM = least squares mean; LSMD = least squares mean difference; LUM/IVA = lumacaftor/ivacaftor; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; NA = not applicable; NR = not reported; OR = odd ratio; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; SD = standard deviation; SE = standard error; VAS = visual analogue scale.

[a] 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.

[b] 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).[1,2]

[c] 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%).[1,2]

[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.[1,2]

[e] Calculated using a Cox proportional-hazards regression analysis with adjustment for sex, age group (< 18 versus ≥ 18 years), and $ppFEV_1$ at screening (< 70% versus ≥ 70%).[1,2]

Sources: Wainwright et al., 2015,[3] Common Technical Document sections 2.7.4[4] and 5.3.5.3,[5] and Clinical Study Reports.[1,2]

Table 2: Summary of Key Efficacy Results for Patients Aged Six Years to 11 Years

	Study 109		Study 11B
	Placebo N = 101	L200/IVA N = 103	L200/IVA N = 58
Absolute Change From Baseline in ppFEV$_1$ Through 24 Weeks			
Baseline, mean (SD)	90.7 (10.8)	88.8 (13.7)	91.4 (13.7)
LSM (SE)	–1.3 (0.8)	1.1 (0.8)	1.0 (1.1)[d]
LSMD (95% CI)	2.4 (0.4 to 4.4)[a]		NA
P value	0.0182		0.3942
Relative Change From Baseline in ppFEV$_1$ Through 24 Weeks			
Baseline, mean (SD)	90.7 (10.8)	88.8 (13.7)	91.4 (13.7)
LSM (SE)	–0.9 (1.0)	2.2 (1.0)	1.8 (1.5)[d]
LSMD (95% CI)	3.2 (0.6 to 5.7)[a]		NA
P value	0.0141		0.2539
Absolute Change From Change From Baseline in LCI$_{2.5}$ Through 24 Weeks			
Baseline, mean (SD)	10.26 (2.24)	10.30 (2.36)	9.99 (2.67)
LSM (SE)	0.08 (0.13)	–1.01 (0.13)	–0.97 (0.21)[d]
LSMD (95% CI)	–1.09 (–1.43 to –0.75)[a]		NA
P value	< 0.0001		0.0002
Absolute Change From Change From Baseline in BMI-for-Age Z Score			
Baseline, mean (SD)	−0.14 (0.88)	−0.14 (0.84)	0.01 (0.90)
LS mean (SE)	0.05 (0.04)	0.08 (0.04)	0.15 (0.04)[d]
LSMD (95% CI)	0.03 (−0.07 to 0.13)[a]		NA
P value	0.5648		< 0.0001
Absolute Change From Baseline in CFQ-R (Respiratory Domain) (Patients)			
Baseline, mean (SD)	77.1 (15.5)	78.7 (14.0)	78.3 (14.9)
LSM (SE)	3.0 (1.0)	5.5 (1.0)	5.4 (2.0)[d]
LSMD (95% CI)	2.5 (–0.1 to 5.1)[a]		NA
P value	0.0628		0.0085
Absolute Change From baseline in CFQ-R (Respiratory Domain) (Parents/Caregivers)			
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
LSM (SE)	[redacted]	[redacted]	[redacted]
LSMD (95% CI)	[redacted]		[redacted]
P value	[redacted]		[redacted]
Pulmonary Exacerbation Through 24 Weeks			
Patients with events, n (%)	[redacted] (14.9)	[redacted] (19.4)	[redacted]
Number of events	18	24	NA
Events per patient-year (95% CI)	[redacted]	[redacted]	
OR, 95% CI	[redacted]		
Rate ratio, 95% CI	[redacted]		
P value versus placebo	[redacted]		
Time-to-First Pulmonary Exacerbation			
Patients with event, n (%)	[redacted] (14.9%)	[redacted] (19.4%)	NA
Event-free probability (95% CI)[c]	0.849 (0.761 to 0.906)	0.800 (0.707 to 0.866)	
Time-to-First Hospitalization for Pulmonary Exacerbation			
Patients with event, n (%)	[redacted]	[redacted]	NA
Event-free probability (95% CI)[c]	[redacted]	[redacted]	

	Study 109		Study 11B L200/IVA N = 58
	Placebo N = 101	L200/IVA N = 103	
Time-to-first Pulmonary Exacerbations Requiring IV Antibiotic Therapy			
Patients with event, n (%)	[redacted]	[redacted]	NA
Event-free probability (95% CI)[c]	[redacted]	[redacted]	

BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire – Revised; CI = confidence interval; IV = intravenous; LCI = lung clearance index; LSM = least squares mean; LSMD = least squares mean difference; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hour; NA = not applicable; OR = odds ratio; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; SD = standard deviation; SE = standard error.

Sources: Clinical study reports.[6,7]

[a] Mixed-effects model for repeated measures (MMRM) that included adjustment for weight (< 25 kg versus ≥ 25 kg), $ppFEV_1$ at screening (< 90% versus ≥ 90%), and baseline value of the end point.

[b] Regression analyses for a negative binomial distribution with weight (< 25 kg versus ≥ 25 kg) and $ppFEV_1$ severity at screening (< 90% versus ≥ 90%) as covariates.

[c] Kaplan–Meier methods to estimate cumulative exacerbation-free survival rates by treatment.

[d] MMRM that included change from baseline in the end point of interest as the dependent variable; patient as random effect; treatment, visit, and treatment-by-visit interaction as fixed effects, with adjustment for sex, weight (< median versus ≥ median) and $ppFEV_1$ at screening (< 70% versus ≥ 70%), and baseline value of the end point.

Table 3: Summary of Adverse Events

Adverse Events, n (%)	≥ 12 years				6 Years to 11 Years		
	TRAFFIC and TRANSPORT		Study 112		Study 109		Study 11B
	Placebo (N = 370)	L400/IVA (N = 369)	Placebo (N = 36)	L400/IVA (N = 34)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Any AEs	355 (95.9)	351 (95.1)	35 (97.2)	30 (88.2)	98 (97.0)	98 (95.1)	55 (94.8)
AEs leading to discontinuation	6 (1.6)	17 (4.6)	0	2 (5.9)	2 (2.0)	3 (2.9)	2 (3.4)
AEs leading to interruption	25 (6.8)	22 (6.0)	0	1 (2.9)	3 (3.0)	9 (8.7)	6 (10.3)
Grade 3 or 4 AEs	59 (15.9)	45 (12.2)	2 (5.6)	6 (17.6)	8 (7.9)	3 (2.9)	4 (6.9)
SAEs	106 (28.6)	64 (17.3)	0	2 (5.9)	11 (10.9)	13 (12.6)	4 (6.9)
AEs leading to death	0	0	0	0	0	0	0

AE = adverse events; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hour; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; SAEs = serious adverse events.

Sources: Common Technical Document section 2.7.4,[4] Clinical study reports.[1,2,6-8]

Introduction

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.[9,10] It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which is located on chromosome seven. The CFTR gene encodes a chloride channel that regulates ion and fluid transport across cell membranes.[9,10] When CFTR is dysfunctional, secretions become tenacious and sticky, resulting in pathology in multiple organs, including the lungs, large and small intestines, pancreatic and bile ducts, and the vas deferens.[9] A deletion of phenylalanine 508 in the first nucleotide binding domain (NBD1) (F508del) is the most common mutation that results in CF.[11,12] According to the Canadian CF Registry, 48.6% of the 4,175 patients with CF in the registry were homozygous for the F508del mutations and 89.2% of the patients had at least one F508del mutation.[13]

More than 1,900 CFTR variants have been identified among patients with CF.[9,10] 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).[9] 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.[9] 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. F508del defect causes CFTR to misfold and thus the majority of the protein is removed before it can reach the cell membrane. In addition, the F508del CFTR presents a defect in channel gating as well as being unstable and having more rapid turnover at the cell membrane.[14,15] Genotyping for mutations in the CFTR gene is routinely performed on almost all patients with CF in Canada and is also part of the newborn screening process.

CF results in airway obstruction, chronic endobronchial infection, and inflammation, which ultimately lead to destruction of lung tissue through development of bronchiectasis and loss of lung function.[16] Lung disease accounts for 85% of mortality[16] in Canadians with CF, whose median age of survival was estimated to be 50.9 years in 2013 and 53.3 years in 2016.[12,13] Chronic endobronchial infection of the airways with bacterial pathogens, such as *Pseudomonas aeruginosa* (which occurs in almost half of individuals with CF[12]) is associated with a more rapid loss of lung function.[17] Acute or chronic endobronchial infections result in further destruction of lung tissue and are associated with respiratory morbidity. Maintenance of pulmonary function (higher forced expiratory volume in one second [FEV_1]) and fewer respiratory exacerbations are associated with increased survival.[18] 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 patients with CF.[19]

Patients who are homozygous for F508del mutation typically have pancreatic, gastrointestinal, and nutritional disease as well as progressive pulmonary damage. Virtually

all of these people will be pancreatic insufficient and will 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.[12]

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* and 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.[20] 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.[21] The median age of death for patients with CF in Canada was 35.1 years in 2013 and 38.9 years in 2016.[12,13] There is a clear unmet need for better CF therapies.

Standards of Therapy

The goals of CF therapy include preservation of lung function by minimizing pulmonary infection and inflammation; restoration of baseline pulmonary function, symptoms, and level of inflammation after acute respiratory exacerbations; and maintenance of adequate nutrition. Respiratory treatments consist of physiotherapy and pharmacologic agents that are antibiotics, anti-inflammatory agents, or mucolytics.[22] Nutritional treatments consist of high calorie and high fat diets[23] 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, 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.[22] 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.

Drug

Indication and Requested Reimbursement Criteria

LUM/IVA is indicated for the treatment of CF in patients aged six years and older who are homozygous for the F508del mutation in the CFTR gene.[24] The manufacturer has requested that lumacaftor/ivacaftor (LUM/IVA) receive a recommendation to reimburse in accordance with the Health Canada–approved indication (Table 4).

Table 4: Indication and Requested Listing Criteria

Indication Under Review
For the treatment of cystic fibrosis in patients aged six years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene.
Reimbursement Criteria Requested by the Applicant
As per indication

Recommended Dosage

The product monograph recommends that LUM/IVA be taken orally with fat-containing food. The recommended dose is:

- ages six to 11: two LUM 100 mg/IVA 125 mg tablets every 12 hours (for a total daily dose of 400 mg LUM and 500 mg IVA)
- ages 12 and older: two LUM 200 mg/IVA 125 mg tablets every 12 hours (for a total daily dose of 800 mg LUM and 500 mg IVA).

The product 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 5).[24] 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.[25]

Table 5: Recommended Dosage Adjustment for Hepatic Impairment

Hepatic Insufficiency	Dose Adjustment	Total Daily Dose
Mild (Child-Pugh Class A)	No dose adjustment	• 6 to 11 years: 400 mg LUM + 500 mg IVA • ≥ 12 years: 800 mg LUM + 500 mg IVA
Moderate (Child-Pugh Class B)	2 tablets (morning) + 1 tablet (evening)	• 6 to 11 years: 300 mg LUM + 375 mg IVA • ≥ 12 years: 600 mg LUM + 375 mg IVA
Severe (Child-Pugh Class C)	1 tablet (morning) + 1 tablet (evening)	• 6 to 11 years: 200 mg LUM + 250 mg IVA • ≥ 12 years: 400 mg LUM + 250 mg IVA

IVA = ivacaftor; LUM = lumacaftor.
Source: Orkambi product monograph.[24]

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 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 with wild-type CFTR. The mechanism of action for LUM/IVA is:[24]

- LUM improves the conformational stability of F508del-CFTR protein, resulting in an increased expression of the F508del-CFTR protein at the cell surface

- IVA increases the channel-open probability of the CFTR protein at the cell surface.

Previous CADTH Reviews

Lumacaftor 400 mg/ivacaftor 250 mg every 12 hours (L400/IVA) was previously reviewed for the treatment of CF in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene and received a do not reimburse recommendation from the CADTH Canadian Drug Expert Committee (CDEC).[26] Ivacaftor alone has been reviewed through the CDR process for the following indications:

- patients years of age and older who have a G551D mutation in the CFTR gene[9]
- patients 6 years of age and older who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R[27]
- patients 18 years of age and older who have an R117H mutation in the CFTR gene.[10]

For each of these indications, CDEC recommended that ivacaftor be listed with clinical criteria and/or conditions.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of LUM/IVA for the treatment of patients aged six years and older with CF who are homozygous for the F508del mutation in the CFTR gene.

Methods

Systematic Review

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Additional studies were selected for inclusion based on the selection criteria presented in Table 6.

Table 6: Inclusion Criteria for the Systematic Review

Patient Population	Patients aged six years and older with 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 200 mg/IVA 250 mg every 12 hours (orally) for patients six years to 11 years • LUM 400 mg/IVA 250 mg every 12 hours (orally) for patients 12 years and older
Comparators	• Standard of care (may include antibiotics, anti-inflammatory drugs, mucolytic drugs, pancreatic enzymes, and physiotherapy) • Placebo
Outcomes	**Efficacy outcomes:** • Mortality or survival • Need for lung transplantation • Disease progression (based on FEV_1 or lung clearance index)[a] • Acute pulmonary exacerbations or infection[a] • Symptoms • Health-related quality of life[a] • Function capacity (e.g., ability to work or attend school)[a] • Hospitalization[a] • Body mass index[a] **Harms outcomes:** • Adverse events, serious adverse events, withdrawals due to adverse events • Notable harms: hepatic adverse events, respiratory adverse events, ophthalmic adverse events
Study Design	Published and unpublished randomized controlled trials (excluding studies phase II and below, if not considered pivotal)

CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; FEV_1 = forced expiratory volume in one second; IVA = ivacaftor; LUM = lumacaftor

[a] These outcomes were identified as important to patients from the patient input.

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 ALL (1946–) 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 concept was Orkambi (lumacaftor/ivacaftor).

No methodological filters were applied to limit retrieval to study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on March 20, 2018. Regular alerts were established to update the search until the meeting of CDEC on July 18, 2018. 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; and databases. 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 CADTH 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 7 and Table 8.

Supplemental Information

CADTH also conducted a literature review to identify supplemental studies that did not meet the inclusion criteria for the systematic review, but addressed key gaps in the evidence from the included studies, and in particular, the gaps identified by CDEC in the previous CADTH review of L400/IVA in patients 12 years of age or older.[26] The key gaps included:

- safety and efficacy in patients with CF with severe lung disease (i.e., per cent predicted FEV_1[$ppFEV_1$] < 40%) or those younger than 12 years of age
- longer-term outcomes such as disease progression, need for lung transplantation, the ability to discontinue other therapies, or mortality.

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

The inclusion criteria for patients, interventions, comparators, and outcomes were the same as those listed in Table 6. Additional inclusion criteria were studies that addressed the key gaps, and were clinical trials (phase II or higher with randomized or non-randomized study designs) that did not meet the systematic review inclusion criteria, or prospective comparative observational studies. Three studies met the inclusion criteria: Study 106 (Appendix 4),[28,29] the PROGRESS extension study (Appendix 5),[30,31] and extension Study 110 (Appendix 6).[32]

Results

Findings from the Literature

A total of five studies were identified from the literature for inclusion in the systematic review (Figure 1).

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

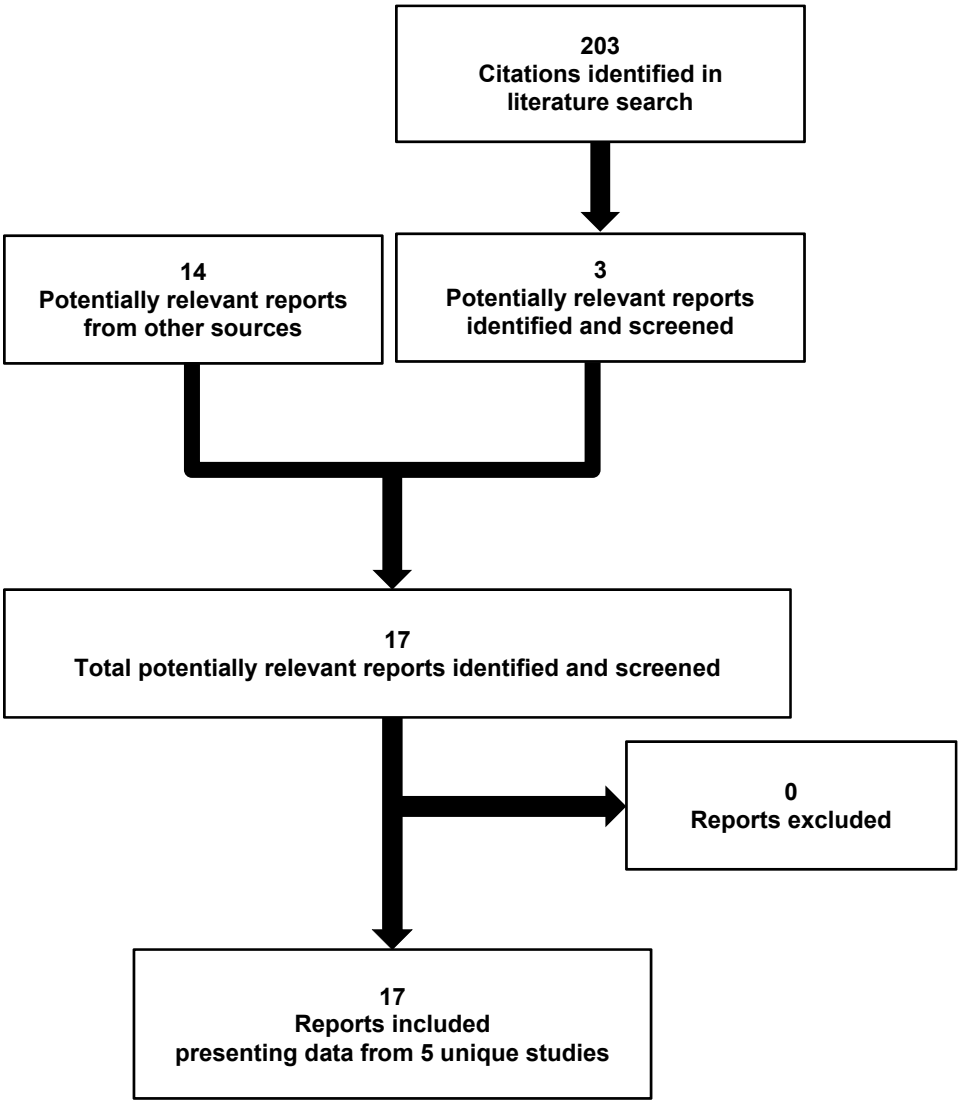


Table 7: Details of Included Studies for Patients 12 Years and Older

		TRAFFIC	TRANSPORT	VX15-809-112 (Study 112)
Designs and Populations	**Study design**	phase III, placebo-controlled, DB RCT	phase III, placebo-controlled, DB RCT	Phase 4, placebo-controlled, DB RCT
	Locations	North America, Europe, and Australia (96 sites)	North America, Europe, and Australia (91 sites)	Australia (13 sites)
	Randomized (N)	559 (1:1:1)	563 (1:1:1)	70 (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 two CF-causing mutations AND ○ chronic sinopulmonary disease OR gastrointestinal or nutritional abnormalities • Homozygous for the F508del-CFTR mutation • FEV_1 ≥ 40% and ≤ 90% of predicted normal for age, sex, and height • Stable CF disease in the opinion of the investigator • Willing to remain on a stable CF medication		• Males and females, aged 12 years or older • Confirmed diagnosis of CF, defined as sweat chloride value ≥ 60 mmol/L • Homozygous for the F508del-CFTR mutation • FEV_1 ≥ 40% and ≤ 90% of predicted normal for age, sex, and height • Stable CF in the opinion of the investigator • 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 four 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*, *Burkholderia dolosa*, or *Mycobacterium abscessus* • Any of the following abnormal laboratory values: ○ hemoglobin < 10 g/dL ○ abnormal liver function defined as any three 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 ≥ 18 years and ≤ 45 mL/min/1.73 m^2 for 12 years to 17 years.		
Drugs	**Intervention**	• LUM 600 mg once daily + IVA 250 mg once every 12 hours[a] • LUM 400 mg once every 12 hour + IVA 250 mg once every 12 hours		LUM 400 mg once every 12 hour + IVA 250 mg once every 12 hours
	Comparator(s)	Matching placebo		Matching placebo
	Phase			
	Screening	28 days	28 days	28 days
	Double-blind	24 weeks	24 weeks	24 weeks
	Follow-up	4 weeks	4 weeks	4 weeks

		TRAFFIC	TRANSPORT	VX15-809-112 (Study 112)
OUTCOMES	**Primary end point**	Absolute change from baseline in $ppFEV_1$ at 24 weeks		Percentage change from baseline in $VO2_{max}$ during cardiopulmonary exercise testing

	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
				• Change from baseline in exercise duration during CPET
				• Change from baseline in oxygen consumption at anaerobic threshold
				• Change from baseline in functional VO_{2max} gain
				• Change from baseline in the pulmonary ventilation versus carbon dioxide production slope
				• Change from baseline in per cent $ppFEV_1$
				• Change from baseline in BMI
				• Change from baseline in CFQ-R respiratory domain
				• Change from baseline in overall Patient Health Questionnaire (PHQ-8) and Generalized Anxiety Disorder (GAD-7) scores
				• Change from baseline in physical activity
				• Change from baseline in duration of sleep time
				• Change from baseline in sleep quality

NOTES	**Publications**[b]	• Wainwright et al., 2015[33] • Clinical study report[1]	• Wainwright et al., 2015[33] • Clinical study report[2]	• Unpublished

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire – Revised; CFTR = cystic fibrosis transmembrane conductance regulator; CPET = cardiopulmonary exercise testing; DB = double blind; EQ-5D-3L = EuroQol 5-Dimension 3-Levels; FEV_1= forced expiratory volume in one second; GFR = glomerular filtration rate; GGT = gamma-glutamyl transferase; IVA = ivacaftor; LUM = lumacaftor; $ppFEV_1$= per cent predicted forced expiratory volume in one second; RCT = randomized controlled trial; TSQM = Treatment Satisfaction Questionnaire for Medication; ULN = upper limit of normal; VAS = visual analogue scale; VO_{2max} = maximal oxygen consumption.

[a] In accordance with the Health Canada–approved dosage regimen for LUM/IVA, CADTH's systematic review focused on the results for LUM 400 mg once every 12 hours/IVA 250 mg once every 12 hours; therefore, data for the LUM 600 mg once daily/IVA 250 mg once every 12 hours dosage regimen are not summarized.

[b] Five additional reports were included: clinical study reports,[1,2,8] Common Technical Document,[4,34] and Clinicaltrials.gov.[35-37]

Table 8: Details of Included Studies for Patients Six Years to 11 Years

		VX14-809-109 (Study 109)	Study 011
Designs and Populations	**Study design**	phase III, placebo-controlled, multicenter, DB RCT	Open-label, 2-part, multicenter (pivotal safety)
	Locations	54 sites in 9 countries (US, Australia, Belgium, Canada, Denmark, France, Germany, Sweden, and UK)	Part A: 6 sites in the US[a] Part B: 20 sites in North America
	Randomized (N)	206 (104 LUM/IVA; 102 placebo)	58 (non-randomized)
	Inclusion criteria	• Ages six years to 11 years • CF with F508del-CFTR mutation on both alleles; chronic sinopulmonary disease OR gastrointestinal or nutritional abnormalities • Stable CF as determined by investigator • Weight ≥ 15 kg • $ppFEV_1 \geq 70$ • $LCI_{2.5} \geq 7.5$	• Ages six years to 11 years • CF with F508del-CFTR mutation on both alleles; chronic sinopulmonary disease OR gastrointestinal or nutritional abnormalities • Stable CF as determined by investigator • Weight ≥ 15 kg • $ppFEV_1 \geq 70$ (Part A) or ≥ 40 (Part B) • $LCI_{2.5} \geq 7.5$

	Exclusion criteria	• 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
		• History of solid organ or hematological transplantation
		• Use of strong or moderate inducers, or strong inducers of CYP450 3A within 14 days
		• Any of the following laboratory values:
		  ○ hemoglobin < 10 g/dL
		  ○ abnormal liver function defined as any three 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 ≤ 45 mL/min/1.73 m^2
			• 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
			• 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*, *Burkholderia dolosa*, or *Mycobacterium abscessus*
			• Use of strong or moderate inducers, or strong inducers of CYP450 3A within 14 days
			• Any of the following laboratory values:
			  ○ hemoglobin <10 g/dL
			  ○ abnormal liver function defined as any three 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 ≤ 45 mL/min/1.73 m^2

Drugs	**Intervention**	LUM/IVA (100 mg/125 mg) (2 tablets every 12 hours)	LUM/IVA (100 mg/125 mg) (2 tablets every 12 hours)
	Comparator(s)	Placebo	No comparator
	Phase		
	Screening	Up to 28 days	Up to 28 days
	Double-blind	24 weeks	Part A: 14 days; Part B: 24 weeks
	Safety follow-up	3 weeks to 5 weeks	3 weeks to 5 weeks
	Extension	96 weeks	96 weeks
Outcomes	**Primary end point**	Mean absolute change from BL in $LCI_{2.5}$	Safety and tolerability
	Other end points	• Average absolute change in sweat chloride concentration from BL to day 15 and week 4 • Absolute change in BMI and BMI-for-age z score (24 week average) • Absolute change in CFQ-R respiratory domain from BL (24 week average) • Absolute change in $LCI_{5.0}$ (24 week average)	• Average absolute change from BL in sweat chloride at day 15 and at week 4 • Absolute change from BL in BMI and BMI-for-age z score at week 24 • Absolute change from BL in weight and weight-for-age z score at week 24 • Absolute change from BL in height and height-

		VX14-809-109 (Study 109)	Study 011
		• Absolute and relative change in ppFEV$_1$ (24 week average) • Change from BL in weight and height • Z scores for weight and height • Absolute change in TSQM domains (24 week average) • Time-to-first pulmonary exacerbation • At least one pulmonary exacerbation • Number of pulmonary exacerbations • Adverse events	for-age z score at week 24 • Absolute change from BL in CFQ-R respiratory domain score at week 24 • Absolute change from baseline in TSQM domains at week 24 • Absolute change in sweat chloride from week 24 to week 26
NOTES	**Publications**[b]	• Ratjen et al., 2017[38]	• Milla et al., 2017[39]

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BL = baseline; BMI = body mass index; CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire – Revised; DB = double blind; EQ-5D-3L = EuroQol 5-Dimension 3-Levels; GFR = glomerular filtration rate; GGT = gamma-glutamyl transferase; IVA = ivacaftor; LCI = lung clearance index; LUM = lumacaftor; ppFEV$_1$= per cent predicted forced expiratory volume in one second; RCT = randomized controlled trial; TSQM = Treatment Satisfaction Questionnaire for Medication; ULN = upper limit of normal.

[a] Part A was a 14-day phase I study used to select the dosage for use in Part B.

[b] Five additional reports were included: clinical study reports,[6,7] Common Technical Document,[40] and Clinicaltrials.gov.[41,42]

Included Studies

Description of studies

Table 9 provides an overview of the studies that were summarized and appraised by CADTH for the current review of LUM/IVA. There were five studies included in the CADTH systematic review: two studies conducted in patients aged six years to 11 years and three studies in patients aged 12 years and older. For patients aged six years to 11 years, there was one placebo-controlled randomized controlled trial (RCT) (Study 109) and one single-arm, pivotal study (Study 11B; considered pivotal by Health Canada for evaluating safety) included in the systematic review. For patients aged 12 years and older, there were three RCTs included in the systematic review (TRAFFIC, TRANSPORT, and Study 112).

CADTH also reviewed several additional studies that did not meet the eligibility criteria of the systematic review. These included two long-term extension phase studies (Study 110 in patients aged six years to 11 years and PROGRESS in patients 12 years and older). In addition, CADTH reviewed Study 106, which was a single-arm study conducted in patients with severe lung disease (i.e., ppFEV$_1$ < 40% at screening).

Table 9: Summary of Studies

Population	Study ID	Design	Duration	Status
Studies Included in Systematic Review				
Ages 6 to 11	VX-809-011B	Pivotal (single-arm)	24 weeks	Complete
	VX-809-109	RCT	24 weeks	Complete
Ages 12 and older	TRAFFIC	RCT	24 weeks	Complete
	TRANSPORT	RCT	24 weeks	Complete
	VX15-809-112	RCT	24 weeks	Complete
Other Studies Included as Supplemental Information				
Ages 6 to 11	VX-809-110	Extension study of studies 109 and 11B[a]	96 weeks	Ongoing
Ages 12 and older ($ppFEV_1$ <40%)	PROGRESS	Extension study of TRAFFIC and TRANSPORT	96 weeks	Complete
	VX14-809-106	Single-arm	24 weeks	Complete

$ppFEV_1$ = per cent predicted forced expiratory volume in one second; RCT = randomized controlled trial.

[a] Only interim data for patients who completed Study 11B were available at the time of CADTH's review.

Patients Aged 12 and Older

TRAFFIC and TRANSPORT were identically designed phase III, randomized, double-blind (DB), placebo-controlled studies conducted to evaluate the efficacy and safety of LUM/IVA in patients with CF at least 12 years of age who are homozygous for the F508del-CFTR mutation. As shown in Figure 2, both studies included a screening phase (up to 28 days), a DB treatment period (24 weeks), and a safety follow-up phase (approximately four weeks).[34] The manufacturer reported that the only differences in the designs of TRAFFIC and TRANSPORT were that an ambulatory electrocardiogram was only performed in a subgroup of patients in TRAFFIC and that an intensive pharmacokinetic sampling was only performed in a subgroup of patients in TRANSPORT.[4] Eligible patients were randomized (1:1:1) to one of the following three treatment groups: LUM 600 mg once daily/IVA 250 mg once every 12 hours (L600/IVA); L400/IVA; or placebo. Randomization was performed with an interactive Web response system (IWRS) and was stratified by age (< 18 years versus ≥ 18 years), sex (male versus female), and disease severity as assessed by $ppFEV_1$ (<70% versus ≥70%) at screening.[34] In accordance with the Health Canada–approved dosage regimen for LUM/IVA, CADTH's systematic review focused on the results for L400/IVA; therefore, data for the L600/IVA dosage regimen are not summarized.

Study 112 was a phase 4, randomized, DB, placebo-controlled study conducted to evaluate the effect of treatment with L400/IVA on the manifestations of CF affected by exercise tolerance and training.[37] The study included a screening phase (up to 28 days), a DB treatment period (24 weeks), and a safety follow-up phase (approximately four weeks).[8] Eligible patients were randomized (1:1) to receive either L400/IVA or placebo. Randomization was performed using an IWRS and was stratified by age (< 18 years or ≥ 18 years), sex (male or female), and $ppFEV_1$ at baseline (< 70% or ≥ 70%).[8]

Patients Aged Six Years to 11 Years

Both Study 11 and Study 109 were conducted to evaluate the safety and efficacy of LUM/IVA in patients with CF between the ages of six years and 11 years of age who are homozygous for the F508del-CFTR mutation. Study 109 was a DB, phase III, placebo-controlled RCT. The study included a screening phase (up to 28 days), a DB treatment period (24 weeks), and a safety follow-up phase (approximately four weeks). Eligible patients were randomized (1:1) to receive LUM 200 mg once every 12 hours/IVA 250 mg once every 12 hours (L200/IVA) or placebo. Randomization was performed using an IWRS

and was stratified by body weight (< 25 kg versus ≥ 25 kg) and $ppFEV_1$ (< 90% versus ≥ 90%) at screening. Patients in both the active and placebo groups who completed the study were eligible to be enrolled in a 96-week extension study (Study 110).

Study 11 was a pivotal, open-label, two-part, single-arm study. Part A was a 14-day phase I study used to select the dosage for use in Part B, a 24-week phase III study. In accordance with the systematic review protocol, this review has focused only on Part B of the study (i.e., Study 11B). This phase of the study consisted of a screening phase (up to 28 days), a single-arm treatment period (24 weeks), a two-week washout period, and a safety follow-up phase (approximately two weeks).[6] Patients who completed the study were eligible to be enrolled in the 96-week extension study (Study 110).

Populations

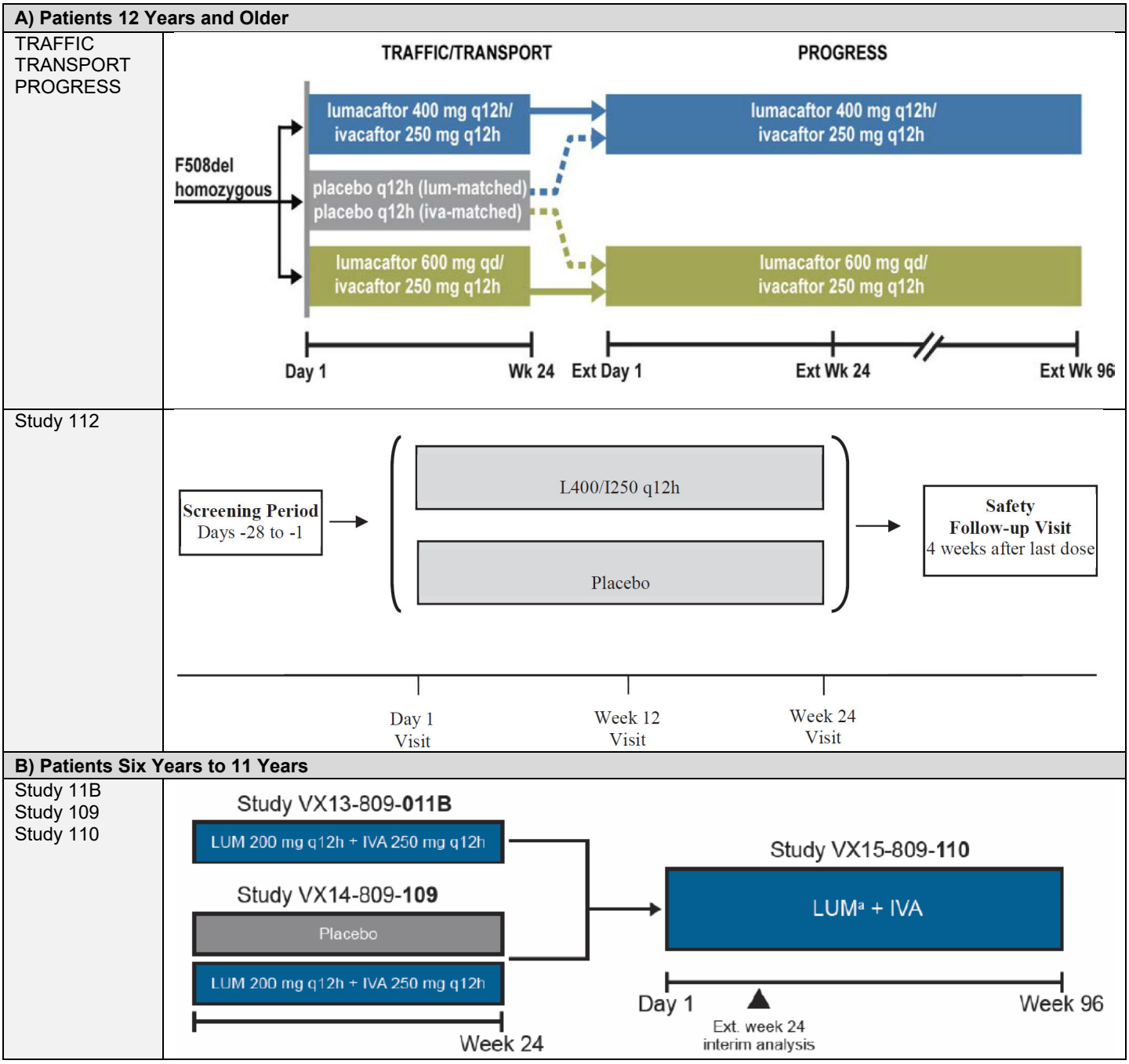
Inclusion and Exclusion Eriteria

Patients 12 Years and Older

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 or nutritional abnormalities. Patients were also required to have stable CF disease (in the opinion of the investigator) and a $ppFEV_1$ of ≥ 40% and ≤ 90% at the time of screening.[34] The trials excluded patients with a history of colonization with Burkholderia cenocepacia, Burkholderia dolosa, 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 the first dose of the 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.[34]

The inclusion criteria for Study 112 were similar to those used in the TRAFFIC and TRANPORT studies, though the diagnostic criteria for confirmed CF were slightly different in Study 112, as patients were only required have a sweat chloride value of ≥ 60 mmol/L (in addition to being homozygous for the F508del-CFTR mutation).[8]

Figure 2: Schematic Showing Design of Studies in Patients 12 Years and Older (A) and Six Years to 11 Years (B)



Ext. = extension; IVA = ivacaftor; L400/I250 = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; LUM = lumacaftor; q12h = every 12 hours; qd = once daily; Wk = week.

Sources: Manufacturer's clinical summary[43] and clinical study report.[8]

Patients Aged Six Years to 11 Years

Patients were eligible for enrolment in studies 11B and 108 if they were between six years and 11 years of age and had a diagnosis of CF with F508del-CFTR mutation on both alleles and either chronic sinopulmonary disease or gastrointestinal or nutritional abnormalities. Patients were required to weigh at least 15 kg and have stable disease (in the opinion of the study investigator). Both studies specified that patients were required to have a lung clearance index ($LCI_{2.5}$) of at least 7.5 to be eligible, but the $ppFEV_1$ were different (at least 70% for enrolment in Study 106 and at least 40% in Study 11B). Exclusion criteria were similar to those used in the TRAFFIC and TRANSPORT studies. Both studies 106 and 11B excluded patients 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 the first dose of the 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. Study 11B excluded patients who had colonization with Burkholderia cenocepacia, Burkholderia dolosa, or Mycobacterium abscessus.[6]

Baseline Characteristics

Patients 12 Years and Older

Table 10 summarizes key baseline and demographic characteristics for the study populations of TRAFFIC, TRANSPORT, and Study 112. The patient characteristics were generally similar across the three studies and across the treatment groups within the studies. In TRAFFIC and TRANSPORT, the majority of participants were recruited from North America (52.6% and 62.4%, respectively). There were 29 patients in TRAFFIC and 14 patients in TRANSPORT who were enrolled at Canadian sites. Study 112, was conducted exclusively in Australia and the UK. Nearly all participants in TRAFFIC and TRANSPORT were white (98.2% and 99.1%, respectively) and all were white in Study 112. The median age of participants was 23 years in TRAFFIC, 24 years in TRANSPORT, and 25 years in Study 112. The proportion of patients who were between the ages of 12 years and 18 years was 28.8% in TRAFFIC, 23.6% in TRANSPORT, and 31.4% in Study 112. There was a slightly greater proportion of males in TRAFFIC than in TRANSPORT (53.7% versus 47.9%; the pooled average was 50.8%).[34] The proportion of males in Study 112 was 55.7% and was greater in the L400/IVA group than in the placebo group (61.8% versus 50.0%).

Mean baseline $ppFEV_1$ was nearly identical in TRAFFIC and TRANSPORT (60.70% [standard deviation (SD): 13.6] and 60.49% [SD: 14.0], respectively) and lower than the values in Study 112 (66.6% [SD: 17.3]). 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. This was lower than in Study 112, where the overall proportion was 34.3% (and was also disproportionate across the placebo and L400/IVA groups [30.6% versus 38.2%], though the difference was only two patients). 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%).[34] In Study 112, 41.1% of patients had $ppFEV_1$ greater than 70% at baseline, with a greater proportion of L400/IVA-treated patients having $ppFEV_1 \geq 70\%$ to $\leq 90\%$ compared with placebo (38.2% versus 30.6%), and a greater proportion of placebo-treated patients having $ppFEV_1$ greater than 90% compared with L400/IVA (11.1% versus 2.9%). Mean baseline body mass index

(BMI) was similar in all three studies (21.25 kg/m^2 [SD: 2.99] in TRAFFIC, 21.10 kg/m^2 [SD: 3.02] in TRANSPORT, and 21.2 kg/m^2 [SD: 2.98] in Study 112). A larger proportion of patients were positive for *P. aeruginosa* in the L400/IVA group (83.0%) compared with the placebo group (72.8%) in TRANSPORT. The proportion of patients who were positive for *P. aeruginosa* was not reported in Study 112.[8]

Table 10: Summary of Demographic and Baseline Characteristics

Characteristics, n (%)		TRAFFIC		TRANSPORT		Study 112	
		Placebo (N = 184)	L400/IVA (N = 182)	Placebo (N = 187)	L400/IVA (N = 187)	Placebo (N = 36)	L400/IVA (N = 34)
Sex, n (%)	Male	100 (54.3)	98 (53.8)	90 (48.1)	89 (47.6)	18 (50.0)	21 (61.8)
	Female	84 (45.7)	84 (46.2)	97 (51.9)	98 (52.4)	18 (50.0)	13 (38.2)
Age (years)	Mean (SD)	25.0 (10.8)	25.5 (10.09)	25.7 (10.02)	25.0 (9.03)	26.1 (10.58)	24.9 (10.17)
	Median (range)	22.0 (12 to 64)	23.5 (12 to 57)	24.0 (12 to 55)	24.0 (12 to 54)	25.5 (12 to 56)	24.5 (12 to 47)
	12 to < 18, n (%)	53 (28.8)	52 (28.6)	43 (23.0)	46 (24.6)	11 (30.6)	11 (32.4)
	≥ 18, n (%)	131 (71.2)	130 (71.4)	144 (77.0)	141 (75.4)	25 (69.4)	23 (67.6)
Race, n (%)	White	183 (99.5)	176 (96.7)	186 (99.5)	185 (98.9)	36 (100.0)	34 (100.0)
	Black	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Asian	0 (0.0)	0 (0.0)	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)	0 (0.0)	0 (0.0)
	Europe	72 (39.1)	75 (41.2)	49 (26.2)	59 (31.6)	NR	NR
	Australia	13 (7.1)	16 (8.8)	16 (8.6)	17 (9.1)	NR	NR
Weight (kg)	Mean (SD)	59.09 (11.7)	60.62 (12.2)	58.46 (13.1)	59.19 (12.1)	60.8 (14.5)	59.8 (15.4)
BMI (kg/m^2)	Mean (SD)[a]	21.03 (3.0)	21.68 (3.2)	21.02 (2.9)	21.32 (2.9)	21.3 (3.05)	21.1 (2.95)
ppFEV$_1$	Mean (SD)	60.45 (13.2)	60.48 (14.3)	60.37 (14.3)	60.59 (14.0)	67.5 (19.33)	65.6 (15.00)
	Min, max	34.0, 88.0	34.8, 94.0	33.9, 99.8	31.3, 96.5	37, 125	41, 101
	< 40	11 (6.0)	12 (6.6)	17 (9.1)	17 (9.1)	1 (2.8)	0
	≥ 40 to < 70	122 (66.3)	116 (63.7)	116 (62.0)	117 (62.6)	20 (55.6)	20 (58.8)
	≥ 70 to ≤ 90	48 (26.1)	51 (28.0)	49 (26.2)	49 (26.2)	11 (30.6)	13 (38.2)
	> 90	0 (0.0)	1 (0.5)	3 (1.6)	2 (1.1)	4 (11.1)	1 (2.9)
FEV$_1$ (L)	Mean (SD)	2.167 (0.62)	2.159 (0.64)	2.136 (0.72)	2.135 (0.62)	2.45 (0.98)	2.38 (0.66)
	Median (range)	2.110 (0.87 to 3.74)	2.095 (0.96 to 3.92)	2.060 (0.79 to 4.68)	2.080 (0.96 to 3.77)	2.26 (1.15 to 5.72)	2.41 (1.31 to 4.07)
P. aeruginosa, n (%)	Positive	134 (72.8)	151 (83.0)	142 (75.9)	135 (72.2)	NR	NR
	Negative	50 (27.2)	31 (17.0)	45 (24.1)	52 (27.8)	NR	NR

BMI = body mass index; FEV$_1$ = forced expiratory volume in one second; LUM400/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; max = maximum; min = minimum; NR = not reported; ppFEV$_1$ = per cent predicted forced expiratory volume in one second; SD = standard deviation.

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

Source: Clinical study reports.[1,2,8]

Patients Aged Six Years to 11 Years

Table 11 summarizes key baseline and demographic characteristics for studies 109 and 11B. All of the participants in Study 11B and the majority of those in Study 109 (58.3%) were from North America. There were 17 patients in Study 109 who were enrolled at Canadian sites (the number of Canadian patients was not reported for Study 11B). All participants in Study 11B were white and nearly all were white in Study 109 (96.1%). The median age of participants was 9.0 years in both studies (range: six to 12). Compared with TRAFFIC and TRANSPORT there was a slightly greater proportion of females in Study 109 (59.3%) and Study 11B (53.4%). Baseline values were similar in studies 109 and 11B for $ppFEV_1$ (89.8% [SD: 12.4] and 91.4% [SD: 13.7], respectively) and BMI (16.46 kg/m^2 [SD: 1.81] and 16.49 kg/m^2 [SD: 1.93], respectively). The patient characteristics were similar between the placebo and L200/IVA groups of Study 109.

Table 11: Summary of Demographic and Baseline Characteristics for Patients Six Years to 11 Years

Characteristics, n (%)		Study 109		Study 11B
		Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Sex, n (%)	Male	43 (42.6)	40 (38.8)	27 (46.6)
	Female	58 (57.4)	63 (61.2)	31 (53.4)
Age at baseline (years)	Mean (SD)	8.9 (1.59)	8.7 (1.60)	9.1 (1.53)
	Median (range)	9.0 (6, 12)	9.0 (6, 12)	9.0 (6, 12)
Race, n (%)	White	96 (95.0)	100 (97.1)	58 (100.0)
	Asian	1 (1.0)	0	0
	Not collected	2 (2.0)	1 (1.0)	0
	Other	2 (2.0)	2 (1.9)	0
Ethnicity, n (%)	Hispanic or Latino	2 (2.0)	0	2 (3.4)
	Not Hispanic or Latino	97 (96.0)	101 (98.1)	56 (96.6)
Region, n (%)	North America	60 (59.4)	59 (57.3)	58 (100)
	Europe	29 (28.7)	28 (27.2)	0
	Australia	12 (11.9)	16 (15.5)	0
Weight	< 25 kg	28 (27.7)	30 (29.1)	4 (6.9)
	≥ 25 kg	73 (72.3)	73 (70.9)	54 (93.1)
	Mean (SD)	30.2 (6.8)	29.4 (6.5)	31.5 (6.1)
	Median (range)	29.3 (20.0 to 51.2)	28.4 (17.7 to 47.4)	30.6 (18.2 to 57.0)
Weight z score	Mean (SD)	–0.21 (0.76)	–0.21 (0.82)	–0.03 (1.03)
	Median (range)	–0.15 (–1.86 to 1.61)	–0.17 (–2.25 to 1.81)	–0.15 (–2.00 to 2.81)
Height (cm)	Mean (SD)	134.4 (10.3)	133.2 (10.8)	136.2 (8.6)
	Median (range)	133.1 (113.8 to 154.0)	133.2 (109.5 to 159.0)	136.2 (111.5 to 156.4)
Height z score	Mean (SD)	–0.16 (0.76)	–0.11 (0.97)	0.03 (1.08)
	Median (range)	–0.10 (–1.91 to 1.87)	–0.09 (–2.29 to 2.52)	0.08 (–2.18 to 2.51)
BMI (kg/m^2)	Mean (SD)	16.55 (1.96)	16.38 (1.66)	16.89 (1.93)
	Median (range)	16.20 (12.72 to 22.73)	16.23 (12.83 to 21.07)	16.49 (13.66 to 23.30)
BMI z score	Mean (SD)	–0.14 (0.88)	–0.14 (0.84)	0.01 (0.90)
	Median (range)	–0.18 (–2.51 to 1.73)	–0.13 (–3.24 to 1.54)	–0.16 (–1.93 to 2.35)
$LCI_{2.5}$	< 7.5	5 (5.0)	3 (2.9)	NR
	≥ 7.5	96 (95.0)	100 (97.1)	NR

Characteristics, n (%)		Study 109		Study 11B
		Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
	Mean (SD)	10.26 (2.24)	10.30 (2.36)	NR
	Median (range)	9.72 (6.55 to 15.82)	9.69 (7.10 to 16.38)	NR
Sweat chloride (mmol/L)	Mean (SD)	103.4 (9.8)	102.6 (10.3)	105.9 (10.2)
	Median (range)	104.6 (64.5 to 123.0)	104.4 (46.0 to 119.0)	107.0 (57.0 to 121.3)
$ppFEV_1$, n (%)	Mean (SD)	90.7 (10.8)	88.8 (13.7)	91.4 (13.7)
	Median (range)	90.7 (70.0 to 114.7)	89.4 (48.6 to 119.6)	90.7 (55.0 to 122.7)
FEV_1 (L)	Mean (SD)	1.59 (0.33)	1.54 (0.38)	1.66 (0.34)
	Median (range)	1.60 (0.90 to 2.48)	1.50 (0.62 to 2.78)	1.64 (0.63 to 2.44)
FVC (L)	Mean (SD)	1.94 (0.40)	1.90 (0.45)	2.01 (0.39)
	Median (range)	1.90 (1.14 to 2.96)	1.84 (0.95 to 3.13)	1.95 (0.85 to 2.94)
P. aeruginosa status, n (%)	Positive	43 (42.6)	44 (42.7)	25 (43.1)
	Negative	58 (57.4)	59 (57.3)	33 (56.9)

BMI = body mass index; FEV = forced expiratory volume; FEV_1 = forced expiratory volume in one second; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; LCI = lung clearance index; NR = not reported; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; SD = standard deviation.

Source: Clinical study reports.[6,7]

Interventions

Patients 12 Years and Older

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); or 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 12. 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.[34] Patients in Study 112 received two tablets of either LUM 200 mg/IVA 125 mg or matching placebo in the morning and in the evening.[8]

Table 12: 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/IVA 250 mg q.12.h	A.M.	–	2	3	–	–	–
	P.M.	–	2	–	–	2	–
LUM 400 mg q.12.h/IVA 250 mg q.12.h	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; q.12.h = once every 12 hours.

Source: Clinical study reports.[1,2]

Patients Aged Six Years to 11 Years

Patients in Study 109 received two tablets of either LUM 100 mg/IVA 125 mg or matching placebo in the morning and in the evening.[28] Study 11B had the same administration schedule with all patients receiving two tablets of LUM 100 mg/IVA 125 mg in the morning and in the evening.[6]

Outcomes

Table 13 provides an overview of key efficacy end points from the included studies. Details regarding the end points of interest for this review are summarized in Appendix 3.

Table 13: Key Efficacy End Points

End Point	Time Point	Patients ≥ 12 Years			Patients 6 Years to 11 Years	
		TRAFFIC	TRANSPORT	Study 112	Study 109	Study 11B
Spirometry						
Abs change in $ppFEV_1$	Avg. wk 16-24	Primary	Primary	NA	NA	NA
	Through wk 24	NA	NA	NA	Secondary	Secondary
	At wk 24	NA	NA	Secondary	NA	NA
Relative change in $ppFEV_1$	Avg. wk 16-24	Key secondary	Key secondary	NA	NA	NA
	Through wk 24	NA	NA	NA	Secondary	Secondary
	At wk 24	NA	NA	Secondary	NA	NA
≥ 5% relative increase in $ppFEV_1$	Avg. wk 16-24	Key secondary	Key secondary	NA	NA	NA
Lung Clearance Index						
Abs change in $LCI_{2.5}$	24 wks	NA	NA	NA	Primary	Exploratory
Abs change in $LCI_{5.0}$	24 wks	NA	NA	NA	Secondary	Exploratory
Pulmonary Exacerbations						
Number of PEx	Through wk 24	Key secondary	Key secondary	NA	Exploratory	NA
Time-to-first PEx	Through wk 24	Secondary	Secondary	NA	Secondary	NA
At least one PEx	Through wk 24	Secondary	Secondary	NA	Exploratory	NA
Time hospitalization for PEx	Through wk 24	Tertiary	Tertiary	NA	Exploratory	NA
Time IV antibiotics for PEx	Through wk 24	Tertiary	Tertiary	NA	Exploratory	NA
PEx requiring hospitalization	Through wk 24	Tertiary	Tertiary	NA	Exploratory	NA
IV antibiotic for PEx	Through wk 24	Tertiary	Tertiary	NA	Exploratory	NA
Days with PEx	Through wk 24	Tertiary	Tertiary	NA	Exploratory	NA
Days hospitalized for PEx	Through wk 24	Tertiary	Tertiary	NA	Exploratory	NA
Days on IV antibiotics for PEx	Through wk 24	Tertiary	Tertiary	NA	Exploratory	NA
Body Composition						
Abs change in BMI	At 24 wks	Key secondary	Key secondary	Secondary	Key secondary	Secondary
Relative change in BMI	At 24 wks	NA	NA	Secondary	NA	
Abs change in weight	At 24 wks	Additional	Additional	NA	Secondary	Secondary
Abs change in height	At 24 wks	Additional	Additional	NA	Secondary	Secondary
Abs change in BMI z score	At 24 wks	Secondary	Secondary	NA	Secondary	Secondary
Abs change in weight z score	At 24 wks	Additional	Additional	NA	Secondary	Secondary
Abs change in height z score	At 24 wks	Additional	Additional	NA	Secondary	Secondary
Sweat Chloride						

End Point	Time Point	Patients ≥ 12 Years			Patients 6 Years to 11 Years	
		TRAFFIC	TRANSPORT	Study 112	Study 109	Study 11B
Abs change in sweat chloride	Day 15; wk 4	NA	NA	NA	Key secondary	Secondary
	At 24 wks	NA	NA	NA	Secondary	Exploratory
Patient Reported Outcomes						
Abs change in CFQ-R (RD)	At 24 wks	Key secondary	Key secondary	Secondary	Key secondary	Secondary
Abs change in EQ-5D-3L	At 24 wks	Secondary	Secondary	NA	NA	NA
Abs change in TSQM	At 24 wks	Secondary	Secondary	NA	Secondary	Secondary
Abs change in PHQ-8	At 24 wks	NA	NA	Secondary	NA	NA
Abs change in GAD-7	At 24 wks	NA	NA	Secondary	NA	NA
Hospitalizations						
Planned hospitalizations for CF	Through wk 24	Exploratory	Exploratory	NA	Exploratory	Exploratory
Unplanned hospitalizations	Through wk 24	Exploratory	Exploratory	NA	Exploratory	Exploratory
Unplanned hospitalizations (days)	Through wk 24	Exploratory	Exploratory	NA	Exploratory	Exploratory
Time to unplanned hospitalization	Through wk 24	Exploratory	Exploratory	NA	Exploratory	Exploratory
Exercise Capacity						
Change in $VO2_{max}$	NA	NA	NA	Primary	NA	NA
Change in exercise duration	NA	NA	NA	Key secondary	NA	NA
Change in VO_{2max} at anaerobic threshold	NA	NA	NA	Secondary	NA	NA
Change in functional VO_{2max} gain	NA	NA	NA	Secondary	NA	NA
Change in slope of pulmonary ventilation versus CO2 production	NA	NA	NA	Secondary	NA	NA
Change in total daily physical activity	NA	NA	NA	Secondary	NA	NA
Change in duration of sleep	NA	NA	NA	Secondary	NA	NA

Abs = absolute; Avg = average; BMI = body mass index; CF = cystic fibrosis; CFQ-R (RD) = Cystic Fibrosis Questionnaire – Revised (respiratory domain); CO2 = carbon dioxide; EQ-5D-3L = EuroQol 5-Dimension 3-Levels; GAD-7 = Generalized Anxiety Disorder 7-item scale; IV = intravenous; LCI = lung clearance index; NA = not applicable; PEx = pulmonary exacerbation; PHQ-8 = Patient Health Questionnaire; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; TSQM = Treatment Satisfaction Questionnaire for Medication; VO_{2max} = maximal oxygen consumption; wk = week.

Sources: Clinical study reports.[1,2,6-8]

Per Cent Predicted FEV_1

Per cent predicted FEV_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[44] standards for patients in studies 109 and 11B and for a subset of patients in TRAFFIC and TRANSPORT (i.e., females aged 12 years to 15 years and males aged 12 years to 17 years). The Hankinson[45] standards were used for females aged 16 years and older and males aged 18 years and older in TRAFFIC and TRANSPORT.[1,2,34] At the time of this review, there is no established minimal clinically important difference (MCID) for absolute change in $ppFEV_1$ for patients with CF.

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

- Absolute change in $ppFEV_1$: Absolute change from baseline was calculated as post-baseline value minus baseline value.
- Relative change in $ppFEV_1$: Calculated and expressed in percentages as 100 × (post-baseline value – baseline value)/baseline value.[1,2]

Absolute change from baseline in $ppFEV_1$ using the average of weeks 16 and 24 was the pre-specified primary efficacy end point of TRAFFIC and TRANSPORT.[1,2] Absolute change from baseline in $ppFEV_1$ through 24 weeks were secondary efficacy end points of studies 109 and 11B.[6,7] Improvement of ≥ 5% in average relative change from baseline in $ppFEV_1$ at week 16 and week 24 was a pre-specified key secondary end point of TRAFFIC and TRANSPORT.[1,2]

In TRAFFIC and TRANSPORT, 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.

Pulmonary Exacerbations

In TRAFFIC, TRANSPORT, and Study 109, 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% (based on spirometry); or radiographic changes indicative of pulmonary infection. Changes in antibiotic therapy for sinopulmonary signs or symptoms were determined and documented by the study investigator at each study visit.[1,2] If at least four of the previously 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% [based on spirometry], and radiographic changes indicative of pulmonary infection). Changes in sputum, new or increased hemoptysis, increase cough, increased dyspnea, malaise, fatigue or lethargy, and in sinus discharge were independently assessed by the investigator, or together with patient description, evaluated and reported by the investigator. There did not appear to have been an independent adjudication of pulmonary exacerbation events.

The following end points related to exacerbations were evaluated in TRAFFIC, TRANSPORT, and Study 109:[34]

- number of pulmonary exacerbations from baseline to week 24 (key secondary end point in TRAFFIC and TRANSPORT)
- time-to-first pulmonary exacerbation

- proportion of patients with 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
- says on IV antibiotic therapy for pulmonary exacerbation
- time-to-first IV antibiotic therapy for pulmonary exacerbation.[7,34]

Lung Clearance Index

The lung clearance index (LCI) is a multiple-breath washout test that estimates the number of lung volume turnovers required to clear the lung of an inert gas.[46] The test is sensitive to changes in the small airways, and may be able to detect pulmonary disease in patients with normal FEV_1.[47,48] The LCI assessments were derived from multiple-breath washout testing using nitrogen. Absolute change from baseline in $LCI_{2.5}$ was the primary end point of Study 109 and represents the number of lung turnovers that are required to reduce the end tidal nitrogen concentration to 2.5% of the starting value. Each multiple-breath washout assessment was performed three times at the study visit. The baseline and post-baseline assessments of LCI were performed pre-bronchodilator and prior to dosing of the study medications.[7]

Body Mass Index, Weight, and Height

All of the included studies evaluated changes from baseline in BMI, body weight, and height. 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 for patients 12 years to 20 years of age in TRAFFIC and TRANSPORT[34] and all patients in studies 109 and 11B. Absolute change from baseline in BMI was a pre-specified key secondary end point of TRAFFIC, TRANSPORT, and Study 109.[1,2,7]

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.[34] 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.[34] A difference of at least four points in the respiratory domain score of the CFQ-R has been cited as the MCID.[49] Separate versions of the CFQ-R have been created for adolescents and adults, parents and caregivers, children aged six years to 11 years, and children aged 12 years to 13 years.[34] The absolute change from baseline in the CFQ-R respiratory domain score at 24 weeks was a pre-specified key secondary end point in TRAFFIC, TRANSPORT, and Study 109.[1,2,7]

EuroQoL 5-Dimensions 3-Levels Questionnaire

The EuroQoL 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire was a secondary end point in the TRAFFIC and TRANSPORT studies.[1,2] The 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.[34] 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, using the US valuation set. Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1 are assigned to the health states "dead" and "perfect health," respectively. Estimates of the MCID for the EQ-5D range from 0.033 to 0.074.[50] The construct validity and MCID of the EQ-5D have not been formally assessed in CF.
- The EQ visual analogue scale (VAS) of the EQ-5D captures the 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).[51] The MCID for the EQ-5D VAS in patients with CF is uncertain.

Statistical Analysis

Patients 12 Years and Older

TRAFFIC and TRANSPORT

Absolute changes from baseline in $ppFEV_1$ were calculated using a mixed-effects model for repeated measures (MMRM) approach. The model (which included absolute change from baseline in $ppFEV_1$ as the dependent variable; 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.

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 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 conducting 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) were 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 week 16 and week 24 were considered to be nonresponders.

Study 112

Absolute changes from baseline in maximal oxygen consumption ($VO2_{max}$) were calculated using an MMRM approach. The model included percentage change from baseline in $VO2_{max}$ as the dependent variable; patient as random effect; treatment, visit, and treatment-by-visit interaction as fixed effects, with adjustment for sex, age at baseline (< 18 versus ≥ 18 years), $ppFEV_1$ at baseline (< 70% versus ≥ 70%), and $VO2_{max}$ at baseline. 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
- ANCOVA rank-based analysis
- MMRM with $VO2_{max}$ excluding weight.

The statistical evaluation of the continuous secondary end points were conducted using an MMRM similar to that used for the primary analysis, but with the additional of the baseline value for the end point of interest as a covariate.

Patients Aged Six Years to 11 Years

Study 109

Absolute changes from baseline in $LCI_{2.5}$ were calculated using an MMRM approach. The model included percentage change from baseline in $LCI_{2.5}$ as the dependent variable; patient as random effect; treatment, visit, and treatment-by-visit interaction as fixed effects, with adjustment for weight (< 25 kg versus ≥ 25 kg) and $ppFEV_1$ at screening (< 90% versus ≥ 90%), and $LCI_{2.5}$ at baseline. Missing post-baseline values were not imputed for efficacy analyses conducted using the MMRM approach. A sensitivity analysis of the primary end point was performed using an ANCOVA with multiple imputation. The statistical evaluation of the continuous secondary end points was conducted using an MMRM similar to that used for the primary analysis.

For the number of pulmonary exacerbations (overall, and those requiring IV antibiotics or hospitalization) the comparison between L200/IVA and placebo was conducting using regression analyses for a negative binomial distribution with weight (< 25 kg versus ≥ 25 kg) and $ppFEV_1$ severity at screening (< 90% versus ≥ 90%) as covariates. Time-to-first pulmonary exacerbation (any exacerbation, and those requiring IV antibiotics or hospitalization) were analyzed using Kaplan–Meier methods to estimate cumulative exacerbation-free survival rates by treatment.

Study 11B

Absolute changes from baseline in all of the continuous end points were calculated using an MMRM approach. The model included change from baseline in the end point of interest as the dependent variable; patient as random effect; treatment, visit, and treatment-by-visit interaction as fixed effects, with adjustment for sex, weight (< median versus ≥ median) and $ppFEV_1$ at screening (< 70% versus ≥ 70%), and baseline value of the end point. Missing post-baseline values were not imputed for analyses conducted using the MMRM approach. There were no sensitivity analyses conducted.

Table 14: Statistical Analysis of Efficacy End points

End Point	Statistical Model	Adjustment Factors	Sensitivity Analyses
TRAFFIC and TRANSPORT			
Absolute change $ppFEV_1$	MMRM	• sex • age at BL (< 18 vs. ≥ 18 years) • $ppFEV_1$ at screening (<70% vs. ≥70%)	• MMRM with on-treatment measurements only • ANCOVA (multiple imputation)
$ppFEV_1$ responders	Cochran–Mantel–Haenszel	• sex • age at BL (< 18 vs. ≥ 18 years) • $ppFEV_1$ at screening (< 70% vs. ≥ 70%)	• Not reported
Continuous end points (BMI, CFQ-R, EQ-5D-3L, weight, height)	MMRM	• BL value of end point • sex • age at BL (< 18 vs. ≥ 18 years) • $ppFEV_1$ at screening (< 70% vs. ≥ 70%)	
Number of PEx: PEx (IV antibiotics) PEx (hospitalization)	NBR	• sex • age at BL (< 18 vs. ≥ 18 years) • $ppFEV_1$ at screening (< 70% vs. ≥ 70%)	
Time-to-first: PEx (IV antibiotics) PEx (IV antibiotics) PEx (hospitalization)	Cox regression	• sex • age at BL (< 18 vs. ≥ 18 years) • $ppFEV_1$ at screening (< 70% vs. ≥ 70%)	
Study 112			
Absolute change from baseline in $VO2_{max}$	MMRM	• sex • age at BL (< 18 vs. ≥ 18 years) • $ppFEV_1$ at screening (< 70% vs. ≥ 70%) • BL value of end point	• MMRM with on-treatment measurements only • ANCOVA rank-based analysis • MMRM with $VO2_{max}$ excluding weight
Continuous end points	MMRM	• sex • age at BL (< 18 vs. ≥ 18 years) • $ppFEV_1$ at screening (< 70% vs. ≥ 70%) • BL value of end point	• Not reported
Study 109			
$LCI_{2.5}$	MMRM	• BL value of end point • weight (< 25 kg vs. ≥ 25 kg) • $ppFEV_1$ at screening (< 90% vs. ≥ 90%)	• ANCOVA (multiple imputation)
Continuous end points ($ppFEV_1$, BMI, CFQ-R, weight, height)	MMRM	• BL value of end point • sex • $ppFEV_1$ at screening (< 90% vs. ≥ 90%)	• Not reported
Number of PEx PEx (IV antibiotics) PEx (hospitalization)	NBR	• sex • $ppFEV_1$ at screening (< 90% vs. ≥ 90%)	
Time-to-first: PEx IV antibiotics)	Cox regression	• sex • $ppFEV_1$ at screening (< 90% vs. ≥ 90%)	

End Point	Statistical Model	Adjustment Factors	Sensitivity Analyses
PEx (IV antibiotics) PEx (hospitalization)			
Study 11B			
Continuous end points ($ppFEV_1$, BMI, CFQ-R, weight, height)	MMRM	• BL value of end point • sex • $ppFEV_1$ at screening (< 70% vs. ≥ 70%) • BL weight (< median vs. ≥ median)	• Not reported

ANCOVA = analysis of covariance; BL = baseline; BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire – Revised; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; IV = intravenous; LCI = lung clearance index; MMRM = mixed-effects model for repeated measures; NBR = negative binomial regression; PEx = pulmonary exacerbation; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; $VO2_{max}$ = maximal oxygen consumption; vs. = versus.

Sources: Clinical study reports.[1,2,6-8]

Power Calculations

Patients 12 Years and Older

The manufacturer's sample size calculations were identical in both TRAFFIC and TRANSPORT. The sample size was based on absolute change from baseline in $ppFEV_1$ at end point and assumed a treatment difference of mean absolute change from baseline in $ppFEV_1$ of 5% between the active and placebo treatment groups, and a common SD of 8%; a 10% dropout rate; a two-sided, two group, t-test of equal means; and an alpha of 0.025 to address multiplicity across the two doses of LUM/IVA. The manufacturer reported that a total sample size of 501 patients (167 per group) would have approximately 99% power to detect a difference of 5% in absolute change from baseline in $ppFEV_1$ between LUM/IVA and placebo.[1,2] For the TRAFFIC and TRANSPORT studies, the manufacturer reported that the assumed mean changes in $ppFEV_1$ and the assumed SD were based on the results from a phase II study (VX09-809-102).[1,2]

The sample size in Study 112 was based on absolute change from baseline in $VO2_{max}$ during cardiopulmonary exercise test and assumed a common SD of 10%; a 10% dropout rate; a two-sided test; and an alpha of 0.05. The manufacturer reported that 33 patients per group would have approximately 80% power to detect a difference of 7.5% in absolute change from baseline in $VO2_{max}$ between the L400/IVA and placebo groups.[8] The basis of the assumptions that were used in the power calculation was not reported.

Patients Aged Six Years to 11 Years

The sample size for Study 109 (200 patients; 100 per group) was reported to be based on "feasibility considerations." The study had approximately 90% power to detect a treatment difference in absolute change in $LCI_{2.5}$ from baseline through week 24 of 0.68 at a two-sided 0.05 significance level. This was based on the assumptions of an SD of 1.4 and a 10% dropout rate. The manufacturer reported that the assumed SD was based on data from a phase II study (VX10-770-106).[7]

In Study 11B, the primary safety end point was the proportion of patients with adverse events (AEs). The manufacturer planned to enroll 56 patients and, similar to the other studies, assume a 10% dropout rate. With 50 patients completing the trial, Study 11B had a 92.3% or 99.5% chance of observing AEs in at least one patient if the rate of AEs is 5% or 10%, respectively.

Multiplicity Adjustment

Patients 12 Years and Older

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:[33]

- 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 and at CFQ-R respiratory domain in TRANSPORT. All other end points, including subgroup and pooled analyses, were tested at an alpha = 0.025 level without additional adjustment for multiplicity. There were no adjustments for multiple comparisons performed in Study 112.[8]

Patients Aged Six Years to 11 Years

There were no adjustments for multiple comparisons performed in Study 109 or Study 11B.[6,28]

Analysis Populations

The analysis sets that were used to evaluate the safety and efficacy end point in the included studies are summarized in Table 12.

Table 15: Analysis Sets

Patients	Study	Data Set	Description
≥ 12 years	TRAFFIC TRANSPORT	Full analysis set	All efficacy analyses; consisted of patients who received ≥ 1 dose of study drug.
		Per-protocol set	Used for supportive analyses for primary and key secondary end points and consisted of all full analysis set 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	All safety analyses; consisted of all patients who received ≥ 1 dose of study drug.
	Study 112	Full analysis set	All efficacy analyses; consisted of patients who received ≥ 1 dose of study drug.
		Safety set	All safety analyses; consisted of patients who received ≥ 1 dose of study drug.
6 years to 11 years	Study 109	Full analysis set	All efficacy analyses; consisted of patients who received ≥ 1 dose of study drug.
		Safety set	All safety analyses; consisted of patients who received ≥ 1 dose of study drug.
	Study 11B	Full analysis set	All pharmacodynamics analyses and spirometry-related analyses.
		Safety set	All safety analyses; consisted of patients who received ≥ 1 dose of study drug.
		LCI substudy set	All LCI analyses; consisted of patients who received ≥ 1 dose of study drug.

CFTR = cystic fibrosis transmembrane conductance regulator; LCI = lung clearance index; $ppFEV_1$ = per cent predicted forced expiratory volume in one second.
Sources: Clinical study reports.[1,2,6-8]

Subgroup Analyses

Patients 12 Years and Older

In TRAFFIC and TRANSPORT, pre-planned subgroup analyses were conducted for the primary end point and all key secondary end points based on 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 CADTH 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%).

In Study 112, subgroup analyses were conducted for the primary end point based on age (< 18 or ≥ 18 years), baseline $ppFEV_1$ (< 70% or ≥ 70%; baseline $VO2_{max}$ (< median or ≥ 18 median), or sex (female or male).

Patients Aged Six Years to 11 Years

Pre-planned subgroup analyses were performed in Study 109 for the primary efficacy end point (i.e., change from baseline in $LCI_{2.5}$): sex, baseline $ppFEV_1$ (< 90% and ≥ 90%), baseline weight (< 25 kg and ≥ 25 kg), region (North America, Europe, and Australia), prior use of inhaled antibiotic (yes and no), prior use of an inhaled bronchodilator (yes and no), prior use of inhaled hypertonic saline (yes and no), prior use of inhaled corticosteroids (yes

and no), *P. aeruginosa* status at baseline (positive and negative), and prior use of dornase alfa (yes and no). In accordance with the CADTH systematic review protocol, results are summarized for $ppFEV_1$ (< 90% and ≥ 90%).[7]

The following pre-planned subgroups were used in Study 11B: sex, age (< 9 years and ≥ 9 years), $ppFEV_1$ severity at screening and at baseline (< 90% and ≥ 90%), baseline weight (< median and ≥ median), prior use of inhaled antibiotic (yes and no), prior use of inhaled bronchodilator (yes and no), prior use of inhaled bronchodilator , prior use of inhaled hypertonic saline (yes and no), prior use of inhaled corticosteroids (yes and no), *P. aeruginosa* status at baseline (Positive and Negative), and prior use of dornase alpha (yes and no). In accordance with the CADTH systematic review protocol, results are summarized for the subgroups based on age (< 9 years and ≥ 9 years) and $ppFEV_1$ (< 90% and ≥ 90%).[6]

Pooled Analyses

The manufacturer conducted a pre-planned 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).[52] 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).[34,52]

Patient Disposition

Patients 12 Years and Older

Patient disposition was similar in TRAFFIC, TRANSPORT, and Study 112 (Table 16). Discontinuation from the studies was greater in the L400/IVA groups (5.5% to 8.8%) than in the placebo groups (0% to 2.7%). This was primarily due to differences in withdrawals due to adverse events (WDAEs) in TRANSPORT (5.9% versus 1.1%) and Study 112 (5.9% versus 0%). In TRAFFIC, there were also numerically more WDAEs in the L400/IVA group than in the placebo group (3.3% versus 2.2%), but the difference in the overall discontinuation rate was attributable to four L400/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 full analysis sets (FAS) of TRAFFIC and TRANSPORT included nearly all randomized patients (98% to 100% from the placebo groups and 97% to 99% from L400/IVA groups) and the FAS of Study 112 included all patients.

Patients Six Years to 11 Years

The overall proportion of patients who completed treatment was similar in Study 109 and Study 11B (94.6% and 93.1%, respectively). In contrast to the TRAFFIC and TRANSPORT studies, the proportion of patients who completed treatment was similar in the L200/IVA group (94.2%) and placebo group (95.0%) of Study 109. WDAEs were reported for 2.9% and 3.4% of L200/IVA-treated patients in studies 109 and 11B (respectively), which was similar to the proportion reported in the placebo group (2.0%). The FAS data set included 99% of patients in Study 109 and 100% in Study 11B.

Table 16: Patient Disposition

Disposition, n (%)	≥ 12 Years						6 Years to 11 Years		
	TRAFFIC		TRANSPORT		Study 112		Study 109		Study 11B
	Placebo (N = 184)	L400/IVA (N = 182)	Placebo (N = 187)	L400/IVA (N = 187)	Placebo (N = 36)	L400/IVA (N = 34)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Randomized/enrolled[a]	187	187	187	189	36	34	102	104	58
Enrolled but never dosed	3	5	0	2	0	0	1	1	0
Completed treatment	180 (97.8)	172 (94.5)	182 (97.3)	172 (92.0)	36 (100.0)	31 (91.2)	96 (95.0)	97 (94.2)	54 (93.1)
Discontinued treatment	4 (2.2)	10 (5.5)	5 (2.7)	15 (8.0)	0	3 (8.8)	5 (5.0)	6 (5.8)	4 (6.9)
Adverse event	4 (2.2)	6 (3.3)	2 (1.1)	11 (5.9)	0	2 (5.9)	2 (2.0)	3 (2.9)	2 (3.4)
Refused further dosing	0 (0.0)	1 (0.5)	2 (1.1)	1 (0.5)	0	0	2 (2.0)	1 (1.0)	1 (1.7)
Did not meet eligibility criteria	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	0	0	1 (1.0)	1 (1.0)	1 (1.7)
Non-compliance with study drug	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Requires prohibited medication	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Physician decision	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0	0	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	0	0 (0.0)	1 (1.0)	0 (0.0)
Completed study	182 (98.9)	176 (96.7)	185 (98.9)	180 (96.3)	36 (100.0)	31 (91.2)	98 (97.0)	98 (95.1)	54 (93.1)
Discontinued study	2 (1.1)	6 (3.3)	2 (1.1)	7 (3.7)	0	3 (8.8)	3 (3.0)	5 (4.9)	4 (6.9)
Adverse event	2 (1.1)	2 (1.1)	1 (0.5)	2 (1.1)	0	2 (5.9)	0 (0.0)	2 (1.9)	1 (1.7)
Withdrawal of consent	0 (0.0)	2 (1.1)	1 (0.5)	2 (1.1)	0	0	2 (2.0)	1 (1.0)	2 (3.4)
Physician decision	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0	0	0 (0.0)	0 (0.0)	1 (1.7)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	0	0 (0.0)	1 (1.0)	0 (0.0)
Non-compliance	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	2 (1.1)	0 (0.0)	2 (1.1)	0	0	1 (1.0)	1 (1.0)	0 (0.0)
Full analysis set	184	182	187	187	36	34	101	103	58
Per-protocol set	177	176	182	181	NA	NA	NA	NA	NA
Safety set	184	182	187	187	36	34	101	103	58

L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; NA = not applicable.

[a] Study 11B was non-randomized.

Source: Common Technical Document[34] and clinical study reports.[1,2,6-8]

Exposure to Study Treatments

Study Treatments

Patient exposure to the study drugs is summarized in Table 17. The median treatment duration was 168 days across all of the studies. Compliance with the study treatments was evaluated by counting the number of study drugs at each visit and was reported to be 98.9% in TRAFFIC, 98.8% in TRANSPORT, 99.5% in Study 112, 97.9% in Study 11B, and 98.8% in Study 109.[1,2,6-8]

Prior and Concomitant Medications

Patients 12 Years and Older

Table 18 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%) were 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 the study drug (73.4%) compared with L400/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 L400/IVA groups (59.9% to 62.1%) in both TRAFFIC and TRANSPORT.[34]

In Study 112, there were several imbalances between the placebo and L400/IVA groups in the use of concomitant medications, including dornase alfa (91.7% with placebo and 76.5% with L400/IVA) and inhaled corticosteroids (69.4% with placebo and 58.8% with L400/IVA). The overall usage of inhaled bronchodilators was similar in the placebo and L400/IVA groups, but the distribution of regimens was different, with a greater proportion of patients in the L400/IVA group using on a short-acting bronchodilator (50.0% versus 33.3%) and a lower proportion using a long-acting bronchodilator (alone or in combination with a short-acting bronchodilator; 44.1% versus 63.9%).[8]

Patients Six Years to 11 Years

In Study 109, the use of inhaled antibiotic and inhaled corticosteroids was greater in the placebo group than in the L200/IVA group (29.7% versus 19.4% and 46.5% versus 36.9%, respectively). The use of inhaled hypertonic saline was greater in the L200/IVA group (65.0%) than in the placebo group (53.5%).[7] Concomitant use of dornase alfa and inhaled bronchodilators were similar in the L200/IVA and placebo groups.[7] The usage of inhaled bronchodilators and inhaled hypertonic saline was greater in Study 11B (98.3% and 75.9%, respectively) than in Study 109.[6]

Table 17: Summary of Exposure to Study Drugs

Statistic	≥ 12 Years						6 Years to 11 Years		
	TRAFFIC		TRANSPORT		Study 112		Study 109		Study 11B
	Placebo (N = 184)	L400/IVA (N = 182)	Placebo (N = 187)	L400/IVA (N = 187)	Placebo (N = 36)	L400/IVA (N = 34)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Patient-years	83.8	81.1	84.2	82.2	16.7	14.7	45.2	45.2	25.3
Duration (days)									
Mean (SD)	166.4 (13.19)	162.8 (23.64)	164.5 (20.88)	160.6 (31.26)	169.0 (5.62)	157.9 (42.15)	163.3 (24.9)	160.1 (31.9)	159.2 (34.2)
Median (range)	168.0 (32 to 179)	168.0 (2 to 178)	168.0 (7 to 181)	168.0 (1 to 182)	168.0 (161 to 182)	168.5 (3 to 182)	168.0 (5 to 183)	168.0 (9 to 179)	168.0 (11 to 174)
Classification, n (%)									
> 0 to ≤ 2 weeks	0 (0.0)	1 (0.5)	2 (1.1)	5 (2.7)	0	1 (2.9)	1 (1.0)	1 (1.0)	1 (1.7)
> 2 to ≤ 4 weeks	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0	1 (2.9)	1 (1.0)	2 (1.9)	2 (3.4)
> 4 to ≤ 8 weeks	1 (0.5)	4 (2.2)	0 (0.0)	2 (1.1)	0	1 (2.9)	1 (1.0)	1 (1.0)	0
> 8 to ≤ 16 weeks	1 (0.5)	2 (1.1)	1 (0.5)	2 (1.1)	0	0	0	2 (1.9)	0
> 16 to ≤ 24 weeks	150 (81.5)	145 (79.7)	141 (75.4)	145 (77.5)	23 (63.9)	14 (41.2)	73 (72.3)	61 (59.2)	42 (72.4)
> 24 weeks	32 (17.4)	30 (16.5)	42 (22.5)	33 (17.6)	13 (36.1)	17 (50.0)	25 (24.8)	36 (35.0)	13 (22.4)

L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; L400/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; SD = standard deviation.

Source: Common Technical Document section 2.7.3[34] and clinical study reports.[6-8]

Table 18: Prior Use of Medications for Cystic Fibrosis Medications

Prior Medication n (%)	≥ 12 Years						6 Years to 11 Years		
	TRAFFIC		TRANSPORT		Study 112		Study 109		Study 11B
	Placebo (N = 184)	L400/IVA (N = 182)	Placebo (N = 187)	L400/IVA (N = 187)	Placebo (N = 36)	L400/IVA (N = 34)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Dornase alfa	135 (73.4)	123 (67.6)	146 (78.1)	150 (80.2)	33 (91.7)	26 (76.5)	88 (87.1)	88 (85.4)	50 (86.2)
Inhaled antibiotic	122 (66.3)	113 (62.1)	136 (72.7)	112 (59.9)	21 (58.3)	21 (61.8)	30 (29.7)	20 (19.4)	14 (24.1)
Azithromycin	112 (60.9)	97 (53.3)	130 (69.5)	119 (63.6)	21 (58.3)	20 (58.8)	NR	NR	NR
Inhaled bronchodilator	172 (93.5)	171 (94.0)	170 (90.9)	169 (90.4)	35 (97.2)	32 (94.1)	82 (81.2)	85 (82.5)	57 (98.3)
SABD only	76 (41.3)	81 (44.5)	78 (41.7)	73 (39.0)	12 (33.3)	17 (50.0)	64 (63.4)	67 (65.0)	48 (82.8)
SABD and LABD or LABD only	96 (52.2)	90 (49.5)	92 (49.2)	96 (51.3)	23 (63.9)	15 (44.1)	18 (17.8)	18 (17.5)	9 (15.5)
Inhaled hypertonic saline	100 (54.3)	112 (61.5)	120 (64.2)	115 (61.5)	21 (58.3)	19 (55.9)	54 (53.5)	67 (65.0)	44 (75.9)
Inhaled corticosteroids	113 (61.4)	109 (59.9)	107 (57.2)	103 (55.1)	25 (69.4)	20 (58.8)	47 (46.5)	38 (36.9)	25 (43.1)

LABD = long-acting bronchodilator; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; NR = not reported; SABD = short-acting bronchodilator.
Sources: Common Technical Document section 2.7.3[4] and clinical study reports.[6-8]

Critical Appraisal

Internal Validity

Patients 12 Years and Older

Randomization was performed using an appropriate methodology with adequate allocation concealment (i.e., IWRS) and stratification based on relevant prognostic factors (i.e., age, sex, and baseline ppFEV$_1$).[1,2,8] Baseline and demographic characteristics were generally well-balanced across the treatments of each of the studies conducted in patients 12 years of age and older. The only exceptions appeared to be a greater proportion of patients who were positive for *P. aeruginosa* in the L400/IVA group of TRAFFIC compared with placebo (83.0% versus 72.8%), and some regional differences between L400/IVA and placebo in TRANSPORT: a greater proportion of patients in the placebo group were enrolled at North American centres (65.2% versus 59.4%) and, conversely, a greater proportion of patients in the L400/IVA groups were enrolled at European centres (31.6% versus 26.2%).

In both TRAFFIC and Study 112, the manufacturer reported that a greater proportion of patients in the placebo group received dornase alfa before the first dose of the study drug compared with the L400/IVA group (73.4% versus 67.6% in TRAFFIC and 91.7% versus 76.5% in Study 112). This could potentially bias the treatment effect against L400/IVA as the increased use of dornase alfa, a mucolytic agent, could favour placebo participants for respiratory end points. Alternatively, these patients may have had more severe disease that required additional treatment; hence, any potential impact of this imbalance is uncertain. The proportions of study participants who were receiving inhaled antibiotics at baseline was greater in the placebo groups (66.3% to 72.7%) compared with the L400/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 concluded 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).[25]

Study treatments were administered in a DB manner with all groups issued the same number of tablets each day. The active and placebo tablets were identical in appearance. L400/IVA was associated with an increase in some gastrointestinal and respiratory AEs; however, the clinical expert consulted by CADTH 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 DB treatment period. The FAS of TRAFFIC and TRANSPORT included nearly all randomized patients, but were not a true intention-to-treat data set. FDA statistical reviewers noted that the amount of missing data in the two studies was minimal and not a concern.[53] The FAS of Study 112 included all randomized patients. 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

TRAFFIC, TRANSPORT, and Study 112. 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 was the lower usage of IV antibiotics for pulmonary exacerbations, a pre-specified end point, during the trials in the L400/IVA groups compared with the placebo groups.

There are no globally accepted definitions for pulmonary exacerbations in patients with CF.[25] The definitions used in the TRAFFIC and TRANSPORT studies were considered to be appropriate by regulatory authorities and the clinical expert consulted by CADTH. There does not appear to have been an independent adjudication of pulmonary exacerbation events. Exacerbations were only reported as AEs in Study 112 and a definition was not provided.[8]

Statistical power calculations were reported for TRAFFIC, TRANSPORT, and Study 112 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,[8,34] providing additional power to detect differences between the treatment groups.[25] The FDA statistical reviewer noted that the pivotal trials (TRAFFIC and TRANSPORT) 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 L400/IVA is clinically beneficial.[53,54] They noted that a mean absolute change from baseline in $ppFEV_1$ of 1.7% in a phase II study (DISCOVER; N = 140)[55,56] of ivacaftor monotherapy in patients who are homozygous for the F508del mutation was transient and not sustained and was not considered to be a clinically meaningful treatment effect.[53]

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 end point and a limited number of key secondary end points in TRAFFIC and TRANSPORT. 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).[53] 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 hypothesis generating because of the risk of type I error. There were no adjustments for multiple comparisons in s\Study 112;[8] therefore, beyond the analysis of the primary end point, subsequent end points were all at risk of inflated type I errors.

EQ-5D-3L index scores at baseline were relatively high, with approximately half of all patients reporting a score of 1 (i.e., perfect health) at baseline. This creates a ceiling effect and makes 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 patients with CF.

Patients Six Years to 11 Years

Randomization in Study 109 was conducted using an appropriate method with adequate allocation concealment (i.e., IWRS) and was stratified for relevant prognostic factors (i.e., screening values for $ppFEV_1$ [≥ 90% or < 90%] and body weight [< 25 kg versus ≥ 25 kg]). Baseline and demographic characteristics were well-balanced between the L200/IVA and placebo groups.[57] Similar to the TRAFFIC and TRANSPORT studies, the proportion of Study 109 participants who were receiving inhaled antibiotics at baseline was greater in the placebo group (29.7%) than in the L200/IVA group (19.4%). As is the case with those studies, it is uncertain if this difference would have any impact on the results of the study. In addition, the direction and magnitude of any potential confounding due to this difference is uncertain (i.e., whether or not these patients are at greater or lower risk of experiencing deterioration).

Study treatments were administered in a DB manner in Study 109 and open-label in Study 11B. Both the placebo and L200/IVA groups in Study 109 were issued the same number of tablets each day and the active and placebo tablets were identical in appearance. The AEs reported in Study 109 did not demonstrate increases in gastrointestinal and respiratory AEs with L200/IVA (as observed in TRAFFIC and TRANSPORT) and were unlikely to compromise blinding of the study. The LCI, spirometry, and sweat chloride end points were centrally analyzed and without knowledge of the measurements obtained at previous study visits.

Approximately 95% of patients completed the treatment periods in both Study 109 and Study 11B, and the FAS included nearly all randomized or enrolled patients (i.e., > 99%). There was a considerable amount of missing data for the primary end point in Study 109 (16.7% of measurements were missing; generally balanced across the two groups).[57] The manufacturer reported that these were primarily attributable to the absence of two acceptable measurements for some visits (hence the values could not be used). The impact of missing data was investigated by the manufacturer using an ANCOVA model with multiple imputation; the results were supportive of the primary analysis.[57] Overall, the potential impact of missing data for the efficacy end points is minimal and unlikely to compromise the results; however, given the large amount of missing data for the primary end point, bias in the study results cannot be completely ruled out. Missing data were common for the CFQ-R respiratory domain evaluation in Study 109, with baseline measurements only reported for 77% and 75% of patients in the placebo and L200/IVA groups, respectively.

Compliance with the study treatments was evaluated by counting the number of study drugs at each visit and was reported to be 97.9% in Study 11B and 98.8% in Study 109.[6,7] A clinical expert consulted by CADTH noted that, in Canada, there is a high level of adherence to CF treatments in younger patients (e.g., those in the target population of six years to 11 years), noting that these patients are under the care of parents or caregivers who ensure that the prescribed regimens are followed. In accordance with the study protocol, the use of concomitant medications remained stable throughout the treatment period for all treatment groups.

The definition used for pulmonary exacerbation in Study 109 was identical to that used in the TRAFFIC and TRANSPORT studies. A clinical expert consulted by CADTH suggested that the diagnosis and measurement of exacerbations in children is often different than with older patients. It was noted that younger patients with CF are more likely to have viral

exacerbations that may not be associated with the same risks of lung function decline that have been observed in older patients with CF who experience pulmonary exacerbations. Exacerbations were only reported as AEs in Study 11B and a definition was not provided.[6,7]

The assumptions used to estimate the sample size for studies 109 and 11B were well reported and a sufficient number of patients were enrolled. As with TRAFFIC and TRANSPORT, the proportion of patients who withdrew from studies 109 and 11B was below the 10% proportion assumed in the manufacturer's statistical power calculation,[6,7] providing additional power to detect differences between the two groups. Statistical analyses of secondary and exploratory end points in studies 109 and 11B were conducted without adjustment for multiplicity; therefore, the findings should be considered hypothesis generating due to the risk of type I error.

External Validity

Patients 12 Years and Older

The diagnostic criteria used in the screening process for TRAFFIC, TRANSPORT, and Study 112 were consistent with Canadian clinical practice for identifying patients with CF who are homozygous for the F508del-CFTR mutation. Patients with CF 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 they were 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.[34] However, it should be noted that the TRAFFIC and TRANSPORT 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 have demonstrated a $ppFEV_1$ <40% at their baseline evaluation. The data for this small subgroup of patients provides some information on the safety and efficacy of L400/IVA in patients with more severe lung deterioration; however, CADTH has also considered the results of an open-label, phase IIIb, clinical study conducted to evaluate the use of L400/IVA in patients with CF who are homozygous for the F508del-CFTR mutation and are suffering from advanced lung disease (Appendix 4).[58]

A majority of the participants in TRAFFIC and TRANSPORT were from North America (52.6% and 62.4%, respectively); whereas, Study 112 was conducted exclusively in Australia and the UK. The study populations were comprised of almost exclusively white patients (98.2% in TRAFFIC, 99.1% in TRANSPORT, and 100% in Study 112), which is reflective of the majority of patients who would be eligible for treatment with L400/IVA, though the percentage is slightly higher than the proportion reported for the overall CF population in Canada (92% in 2013).[12] The proportion of patients who had mild disease (64.3% in TRAFFIC and TRANSPORT and 58.6% in Study 112) or moderate disease (26.6%in TRAFFIC and TRANSPORT and 41.4% in Study 112) 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.[12]

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 is

likely to be obtained in the longer-term follow-up studies.[25] 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.[25] 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 CADTH 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. Mean baseline BMI was similar in all three studies (21.25 kg/m^2 in TRAFFIC, 21.10 kg/m^2 in TRANSPORT, and 21.2 kg/m^2 in Study 112). These figures are slightly below the estimated national median BMI for adult patients with CF (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, TRANSPORT, and Study 112 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 patients with CF in Canada are infected with *Burkholderia cepacia* complex species (88.2% of whom are adults).[12] The clinical expert consulted by CADTH 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 *Burkholderia 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 *Burkholderia cepacia* complex species.

The proportion of patients in TRAFFIC and TRANSPORT who were positive for *P. aeruginosa* was 74.4% and 77.5% in the placebo and L400/IVA groups, respectively (this was noted reported in Study 112). This is greater than the infection rates reported in the overall Canadian CF population (i.e., 43% in 2013). It was noted by the expert consulted by CADTH that infection with *Pseudomonas 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).[5] However, the clinical expert consulted by CADTH 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 prior to the first dose of study drug. The clinical expert consulted by CADTH noted that, due to the potential for L400/IVA to cause respiratory adverse events during the initiation of treatment, clinicians would not typically start a patient on L400/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 patients with CF with gating mutations (i.e., STRIVE, ENVISION, KONNECTION, and KONDUCT),[59-62] the use of placebo as the comparator is appropriate as LUM/IVA is a novel treatment for patients with CF with F508del-CFTR mutations. All studies compared the addition of L400/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, TRANSPORT, and Study 112 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),[59-61] patients in TRAFFIC, TRANSPORT, and Study 112 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 L400/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), 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).[63] Changes in the primary end point (i.e., absolute change $ppFEV_1$) 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.[64] 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.[25]

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 L400/IVA has the potential to modify the course of disease for patients with CF with F508del-CFTR mutations.[33] The initial CADTH review of L400/IVA considered the 24-week data from the first interim analysis of the PROGRESS extension study, which suggested that patients treated with L400/IVA maintained the effects that were observed in the DB phase of TRAFFIC and TRANSPORT (absolute improvement of 2.5% from baseline; $P < 0.0001$). The current review includes the final 96-week data from PROGRESS, including a post hoc matched-registry cohort analysis. CADTH's summary and appraisal of and additional analysis conducted to evaluate the potential impact of L400/IVA treatment on the slope of decline in lung function is provided in Appendix 5.

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.[1,2] However, the results were similar when the end point was analyzed using only the week 24 data, as required by the EMA.[25] The clinical experts consulted by CADTH and the National Institute for Health and Care Excellence (NICE)[65] both indicated that using the average of multiple time points is a method of reducing variability when evaluating changes in $ppFEV_1$.

As is common in clinical trial settings, patients enrolled in TRAFFIC, TRANSPORT, and Study 112 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 patients with CF 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 L400/IVA. In clinical practice, patients using the typical recommended dosage of LUM/IVA, and 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 (for a total of nine tablets per day). Nevertheless, as previously mentioned, compliance with study treatments was very high throughout the DB treatment period. The clinical expert consulted by CADTH noted that the level of compliance observed in TRAFFIC, TRANSPORT, and Study 112 is not reflective of typical adherence in Canada for adults and adolescents with CF, where compliance with treatments, including orally administered treatments, is considerably lower.[66]

Patients Six Years to 11 Years

The eligibility criteria for Study 109 were considered to be appropriate by the EMA.[57] A greater proportion of the population in Study 109 was female (59.3%), which is not reflective of the Canadian CF population where a majority of patients are male (53.5%).[13] Canadian registry data have indicated that females with cystic fibrosis tend to have poorer long-term survival compared with males,[13] but this is unlikely to affect the generalizability of the results of Study 109, which was a short-term trial conducted in children.[57] Similar to the studies conducted in those 12 years of age and older, the majority of patients six years to 11 years of age that were included in the studies were white and from North America. A clinical expert consulted by CADTH noted that the mean BMI at baseline was a reasonable reflection of the Canadian CF patient population.

The diagnostic criteria used to screen patients for studies 109 and 11B were identical to those used in the TRAFFIC and TRANSPORT studies. As noted previously, these criteria are consistent with Canadian clinical practice for diagnosing patients with CF who are homozygous for the F508del-CFTR mutation. Enrolment in Study 109 was limited to patients with a $ppFEV_1$ of at 70%; hence, it was more restrictive than the 40% threshold that was used in TRAFFIC, TRANSPORT, and Study 11B. The manufacturer did not report why the 70% threshold was selected for Study 109. A clinical expert consulted by CADTH indicated that the exclusion of patients with $ppFEV_1 < 70\%$ does not impact the generalizability of Study 109, as these patients are uncommon in the Canadian pediatric CF population. Data from the Canadian CF Registry (2016) indicate that 53.6% of Canadian children with CF (ages six years to 17 years) have normal lung function (i.e., $ppFEV_1 \geq 90\%$); hence, the median $ppFEV_1$ of 90.5% and 90.7% in studies 109 and 11B (respectively) is likely a reasonable reflection of pediatric patients with CF in Canada. Both studies 109 and 11B specified that patients were required to have an $LCI_{2.5}$ of at least 7.5 to be eligible. This measurement is not used in Canadian practice; therefore, there is some uncertainty regarding the generalizability of the inclusion criteria based on this specific threshold. However, a clinical expert consulted by CADTH suggested that the study population is reflective of Canadian pediatric patients with CF, based on other baseline characteristics.

Study 109 also included a range of outcomes that are considered to be important to patients with CF based on patient group input: respiratory function (i.e., LCI and $ppFEV_1$), nutritional status and growth (e.g., weight, height, and BMI), health-related quality of life (CFQ-R), and clinical events (e.g., pulmonary exacerbations). The primary efficacy end point in Study 109 (i.e., $LCI_{2.5}$) differed from that used in the adolescent and adult trials (i.e., $ppFEV_1$). This is reflective of regulatory guidance, which has noted that spirometry may not be sensitive enough to detect treatment differences in patients with CF who are children.[48] Younger patients with CF may demonstrate spirometry values that are within the normal

range, but there may be underlying structural deficiencies within the lungs that can be detected using alternative evaluations (e.g., LCI).[48,57] Although LCI is used as an end point in clinical studies, it is not routinely used in Canadian clinical practice and the clinical relevance of differences in this end point have not be characterized.[57,67] Both Health Canada and the EMA asked the manufacturer to provide additional information to support the clinical relevance of the improvement in LCI that was reported with L200/IVA treatment. In response, the manufacturer indicated that LCI is correlated with FEV_1.[67,68] The clinical experts consulted by CADTH also indicated that LCI is correlated with FEV_1. A literature review conducted by CADTH found that variable correlation was observed between FEV_1 and LCI in children (Appendix 4).

Patients in the placebo group of Study 109 experienced a –1.3% decrease in $ppFEV_1$ at 24 weeks. The clinical expert consulted by CADTH suggested that this would not be reflective of the decline expected in Canadian patients in this age group and could be due to challenges performing the FEV_1 measurement in a younger patient population. Data from the Canadian CF Registry (2013) suggested that patients with CF undergo a decline in lung function of 0.2% per year between the ages of six years and 11 years.[69]

Unlike the TRAFFIC, TRANSPORT, and Study 11B, patients with a history of colonization with *B. cenocepacia*, *B. dolosa*, or *M. abscessus* were not excluded from Study 109. CF Canada reports that these bacteria are more commonly seen in older patients and only a minority of patients in Study 109 were reported to have colonization with Burkholder species (three patients) or *M. abscessus* (four patients). The proportion of patients in studies 109 and 11B who were positive for *P. aeruginosa* was approximately 43% (in both studies), which is close to the rate reported in the overall Canadian CF population (i.e., 37% in 2016). However, a clinical expert consulted by CADTH noted that the rate of *P. aeruginosa* infection in Study 109 likely exceeds the rate in Canadian pediatric patients with CF, which may be due to the aggressive treatment pursued in Canada to eradicate *P. aeruginosa* infection once detected.

Studies 109 and 11B also 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 the study drug. As noted previously, the clinical expert consulted by CADTH suggested that this is reflective of clinical practice where patients are unlikely to initiate treatment with L200/IVA during or shortly after a pulmonary exacerbation.

The use of a placebo as the comparator in Study 109 is appropriate as L200/IVA is the only treatment approved in Canada for the treatment of patients with CF with F508del-CFTR mutations. The absence of a control group in Study 11B limits the ability to interpret the results of the study. In both studies, L200/IVA (or matching placebo in Study 109) was added to the existing therapeutic regimens used by the patients, which is reflective of how L200/IVA would be administered in clinical practice. A clinical expert consulted by CADTH indicated that the background therapies used in studies 109 and 11B were reasonably reflective of the Canadian CF population. The exceptions were dornase alfa and inhaled antibiotics, where it would be anticipated that the usage would be lower and greater in Canadian practice, respectively. It was noted by the expert that this difference is unlikely to limit the generalizability of the study results.

The 24-week study treatment periods were sufficient for observing treatment differences in the primary end point of Study 109; however, the duration was too short to observe whether or not treatment with L200/IVA has the potential to modify the course of disease for patients with CF with F508del-CFTR mutations.[33] In addition, a clinical expert consulted by CADTH

suggested that 24 weeks is unlikely to enough time to observe meaningful changes in BMI, particularly in a younger patient population who are relatively healthy.

Patients in studies 109 and 11B 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 patients with CF with relatively stable disease.

Efficacy

Forced Expiratory Volume in One Second

Absolute Change in $ppFEV_1$

Patients 12 Years and Older

Treatment with L400/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 4, improvements in $ppFEV_1$ with L400/IVA were observed at the time of the first post-baseline assessment (i.e., day 15) in both TRAFFIC and TRANSPORT and were higher at all time points (Table 32). Results of the sensitivity analyses using MMRM with on-treatment measurements only and ANCOVA with multiple imputation were consistent with the result of the primary analysis (Table 34). As shown in Figure 5, results for $ppFEV_1$ were generally consistent across subgroup analyses based on age (12 years to <18 years or ≥ 18 years), $ppFEV_1$ at screening (< 70% or ≥ 70%) and, $ppFEV_1$ baseline (< 40% or ≥ 40%); however, there were wide CIs in subgroup analyses with small sample sizes, such as ages 12 years to 18 years, $ppFEV_1$ ≥ 70% at screening and < 40% at baseline. In Study 112, there was no statistically significant difference between L400/IVA and placebo for absolute change from baseline in $ppFEV_1$ at 24 weeks (3.4% [95% CI, –1.2 to 8.1]).

Patients Aged Six Years to 11 Years

In Study 109, treatment with L200/IVA resulted in an improvement in $ppFEV_1$ compared with placebo through 24 weeks (least squares mean difference [LSMD]: 2.4% [95% CI, 0.4 to 4.4])). The LSM $ppFEV_1$ decreased in the placebo group by –1.3% (SD: 0.8) through 24 weeks, with a decrease of –1.2% (SD: 0.8) observed as early as day 15 (Figure 4). In contrast, the LSM $ppFEV_1$ increased in the L200/IVA group through 24 weeks by 1.1% (SD: 0.8). Within the L200/IVA group, improvement from baseline was observed as early as day 15. In Study 11B, there was no within-group difference in the absolute change in $ppFEV_1$ (2.5% [95% CI, –0.2 to 5.2]). The comparisons in both studies were not adjusted for multiplicity and should be interpreted accordingly.

Relative Change in $ppFEV_1$

Patients 12 Years and Older

Treatment with L400/IVA was associated with a statistically significant improvement in relative change from baseline in $ppFEV_1$ in the TRAFFIC and TRANSPORT 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 $ppFEV_1$, larger relative changes in $ppFEV_1$ were observed with L400/IVA at all post-baseline study visits (Table 32). As shown in Table 33, results for $ppFEV_1$ were

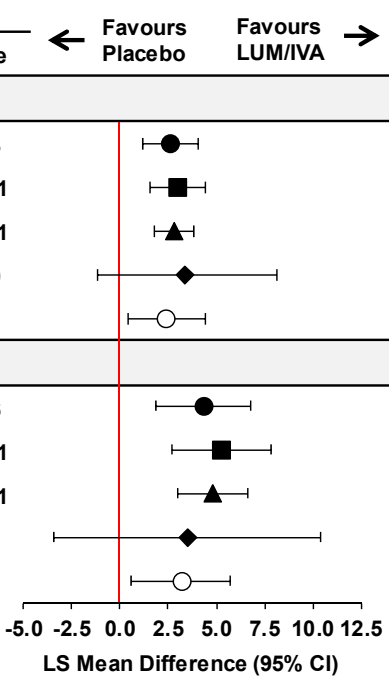
generally consistent across subgroup analyses based on age, $ppFEV_1$ at screening, and $ppFEV_1$ at baseline. Similar to absolute change in $ppFEV_1$, there were wide CIs in the estimated treatment effect for the subgroup analyses with small sample sizes. In Study 112, there was no statistically significant difference between L400/IVA and placebo for absolute change from baseline in $ppFEV_1$ at 24 weeks (3.5% [95% CI, –3.4 to 10.4]).

Patients Aged Six Years to 11 Years

Treatment with L200/IVA as compared with placebo was associated with an improvement in relative change from baseline through 24 weeks in $ppFEV_1$ in Study 109 (3.2% [95% CI, 0.6 to 5.7]) (Figure 3). In Study 11B, there was no within-group difference in relative change in $ppFEV_1$ (1.8% [95% CI, –1.3 to 4.9]). However, these comparisons in both studies were not adjusted for multiplicity and should be interpreted accordingly.

Figure 3: Absolute and Relative Change in $ppFEV_1$ from TRAFFIC, TRANSPORT, Study 112, and Study 109

Age Group	Study	LS Mean Change (SE)		LUM/IVA vs. Placebo	
		Placebo	LUM/IVA	LSMD (95% CI)	P value
Absolute Change from Baseline in $ppFEV_1$					
≥12 Years	TRAFFIC	−0.44 (0.524)	2.16 (0.530)	2.60% (1.18 to 4.01)	0.0003
≥12 Years	TRANSPORT	−0.15 (0.539)	2.85 (0.540)	3.00% (1.56 to 4.44)	<0.0001
≥12 Years	Pooled	−0.32 (0.376)	2.49 (0.379)	2.81% (1.80 to 3.82)	<0.0001
≥12 Years	Study 112	–4.0 (1.65)	–0.6 (1.71)	3.4% (–1.2 to 8.1)	0.1460
6 to 11 Years	Study 109	−1.3 (0.8)	1.1 (0.8)	2.4% (0.4 to 4.4)	0.0182
Relative Change from Baseline in $ppFEV_1$					
≥12 Years	TRAFFIC	−0.34 (0.913)	3.99 (0.923)	4.33% (1.86 to 6.80)	0.0006
≥12 Years	TRANSPORT	0.00 (0.960)	5.25 (0.961)	5.25% (2.69 to 7.81)	<0.0001
≥12 Years	Pooled	−0.17 (0.662)	4.64 (0.666)	4.81% (3.03 to 6.59)	<0.0001
≥12 Years	Study 112	–5.4 (2.44)	–1.8 (2.52)	3.5% (–3.4 to 10.4)	0.3091
6 to 11 Years	Study 109	−0.9 (1.0)	2.2 (1.0)	3.2% (0.6 to 5.7)	0.0141

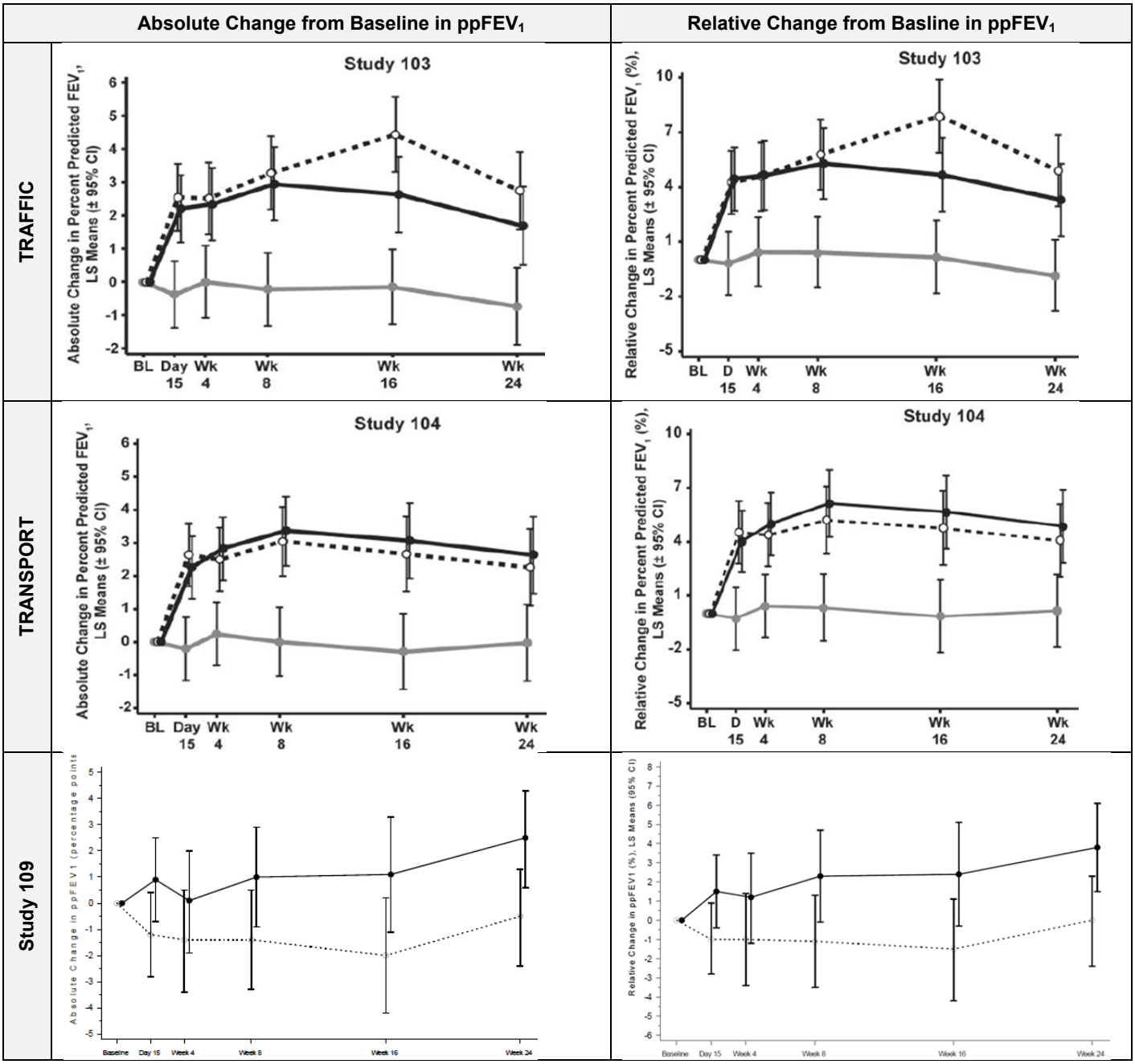


CI = confidence interval; LS = least squares; LSMD = least squares mean difference; LUM/IVA = lumacaftor/ivacaftor; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; SE = standard error; vs. = versus.

Note: Mixed-effects model for repeated measures (MMRM) included treatment, visit, and treatment-by-visit interaction as fixed effects. The model was adjusted for sex (male versus female), age group at baseline (< 18 years versus ≥ 18 years), and $ppFEV_1$ at screening (< 70% versus ≥ 70%) in TRAFFIC and TRANSPORT,[1,2] and weight (< 25 kg versus ≥ 25 kg) and $ppFEV_1$ at screening (< 90% versus ≥ 90%) in Study 109.

Figure shows the absolute and relative change from baseline in $ppFEV_1$ for lumacaftor 400 mg/ivacaftor 250 mg every 12 hours versus placebo for the full analysis sets of TRAFFIC (●), TRANSPORT (▲), the pooled analysis conducted by the manufacturer (■), Study 112 (◆), and for lumacaftor 200 mg/ivacaftor 250 mg every 12 hours versus placebo for the full analysis set of Study 109 (O).

Figure 4: Absolute and Relative Change in ppFEV$_1$ from TRAFFIC, TRANSPORT, and Study 109



BL = baseline; CI = confidence interval; D = day; LS = least squares; FEV$_1$ = forced expiratory volume in one second; Wk = week.

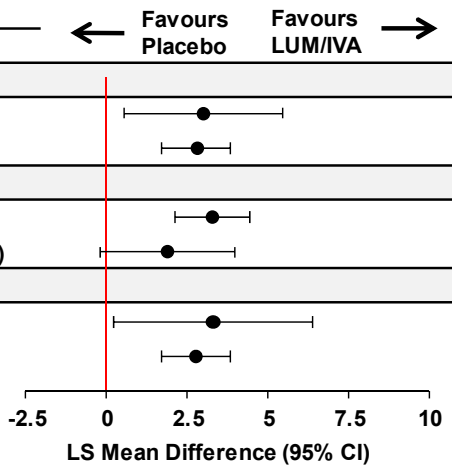
Note: Mixed-effects model for repeated measures (MMRM) included treatment, visit, and treatment-by-visit interaction as fixed effects. The model was adjusted for sex (male versus female), age group at baseline (< 18 versus ≥ 18 years), and per cent predicted FEV$_1$ (PPFEV$_1$) at screening (< 70% versus ≥ 70%) in TRAFFIC and TRANSPORT,[1,2] and weight (< 25 kg versus ≥ 25 kg) and ppFEV$_1$ at screening (< 90% versus ≥ 90%) in Study 109.

This figure shows the absolute and relative change from baseline in ppFEV$_1$ for lumacaftor 600 mg once daily/ivacaftor 250 mg once every 12 hours (○),lumacaftor 400 mg/ivacaftor 250 mg every 12 hours (●), and placebo (●) in TRAFFIC and TRANSPORT; lumacaftor 200 mg/ivacaftor 250 mg every 12 hours (●) and placebo (○) in Study 109.

Source: Clinical study reports.[1,2,7]

Figure 5: Subgroup Analyses for Absolute Change in $ppFEV_1$ in TRAFFIC and TRANSPORT

Subgroup	LS Mean Difference (95% CI) TRAFFIC	TRANSPORT	Pooled
Age			
≥12 to <18 years	4.12 (0.75, 7.50)	1.66 (−1.95, 5.27)	2.98 (0.52, 5.44)
≥18 years	2.02 (0.55, 3.50)	3.46 (1.92, 4.99)	2.79 (1.72, 3.85)
$ppFEV_1$ at screening			
<70%	2.95 (1.33, 4.57)	3.57 (1.89, 5.24)	3.26 (2.10, 4.42)
≥70%	2.19 (−0.81, 5.19)	1.62 (−1.26, 4.50)	1.86 (−0.22, 3.95)
$ppFEV_1$ at baseline			
<40%	1.60 (−4.52, 7.73)	4.37 (0.91, 7.82)	3.30 (0.22, 6.39)
≥40%	2.73 (1.26, 4.20)	2.79 (1.24, 4.34)	2.77 (1.70, 3.84)



CI = confidence interval; LS = least squares; LUM/IVA = lumacaftor/ivacaftor; $ppFEV_1$ = per cent predicted forced expiratory volume in one second.

Note: Mixed-effects model for repeated measures (MMRM) 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%).[1,2]

This figure shows the absolute change from baseline in $ppFEV_1$ for lumacaftor 400 mg/ivacaftor 250 mg every 12 hours in the pooled analysis of TRAFFIC and TRANSPORT.

Source: Data from clinical study reports.[1,2]

FEV_1 Responder Analysis

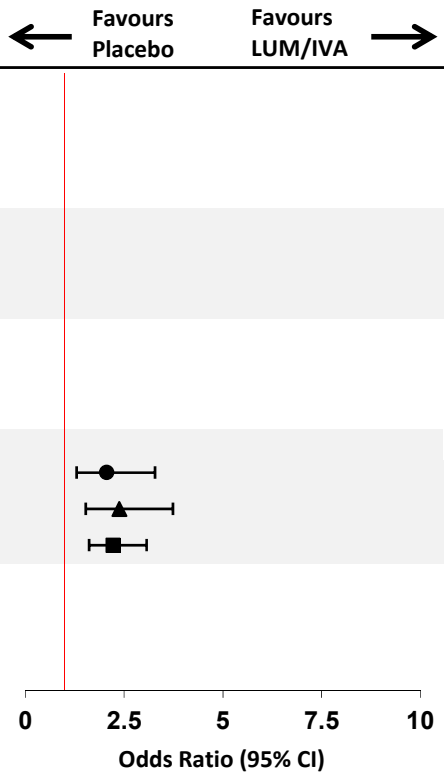
Patients 12 Years and Older

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 TRAFFIC and TRANSPORT 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 inconclusive due to the risk of type I error. Similarly, the statistical tests for the pooled analyses of the different responder analyses were conducted without adjustment for multiplicity and should considered in light of the risk of type I error.

Across both the TRAFFIC and TRANSPORT studies, a greater proportion of L400/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 L400/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 L400/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 $ppFEV_1$ From TRAFFIC and TRANSPORT

Endpoint	Study	Responders; n (%) Placebo	Responders; n (%) LUM/IVA	LUM/IVA vs. Placebo OR (95% CI)
Average Absolute Change in $ppFEV_1$				
≥3% Increase	TRAFFIC	[redacted]	[redacted]	[redacted]
	TRANSPORT	[redacted]	[redacted]	[redacted]
	Pooled	[redacted]	[redacted]	[redacted]
≥5% Increase	TRAFFIC	[redacted]	[redacted]	[redacted]
	TRANSPORT	[redacted]	[redacted]	[redacted]
	Pooled	[redacted]	[redacted]	[redacted]
≥10% Increase	TRAFFIC	[redacted]	[redacted]	[redacted]
	TRANSPORT	[redacted]	[redacted]	[redacted]
	Pooled	[redacted]	[redacted]	[redacted]
Average Relative Change in $ppFEV_1$				
≥5% Increase	TRAFFIC	41 (22.3)	67 (36.8)	2.06 (1.29, 3.28)
	TRANSPORT	42 (22.5)	77 (41.2)	2.38 (1.52, 3.73)
	Pooled	83 (22.4)	144 (39.0)	2.22 (1.61, 3.07)
≥10% Increase	TRAFFIC	[redacted]	[redacted]	[redacted]
	TRANSPORT	[redacted]	[redacted]	[redacted]
	Pooled	[redacted]	[redacted]	[redacted]



CI = confidence interval; LUM/IVA = lumacaftor/ivacaftor; OR = odds ratio; $ppFEV_1$ = per cent predicted forced expiratory volume in one second.

Note: 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%).[1,2]

This figure shows the odds ratios 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.

Source: Data from clinical study reports.[1,2]

Lung Clearance Index

Patients Aged Six Years to 11 Years

As shown in Table 19, treatment with L200/IVA was associated with a statistically significant improvement in $LCI_{2.5}$ compared with placebo (LSMD: –1.09 [95% CI, –1.43 to –0.75]). The within-group LSM absolute change in $LCI_{2.5}$ through 24 weeks was –1.01 compared with an increase of 0.08 in the placebo group. Results were similar in the supportive analysis that was conducted using an ANCOVA with multiple imputation for missing data (LSMD: –1.20 [95% CI, –1.84 to –0.55]). As shown in Figure 7, L200/IVA-treated patients experienced a decrease in $LCI_{2.5}$ beginning at day 15. The results in the subgroup analyses were –1.08 (95% CI, –1.61 to –0.54) in those with $ppFEV_1$ < 90% at baseline and –1.17 (95% CI, –1.60 to –0.73) in those with $ppFEV_1$ ≥ 90% at baseline. $LCI_{5.0}$ also improved in patients treated.

Treatment with L200/IVA was also associated with an improvement in $LCI_{5.0}$ compared with placebo (LSMD: –0.44 [95% CI, –0.57 to –0.31]) through 24 weeks.[8] However, this comparison was not adjusted for multiplicity and should be interpreted accordingly.

Table 19: Change from Baseline in Lung Clearance Index from Study 109

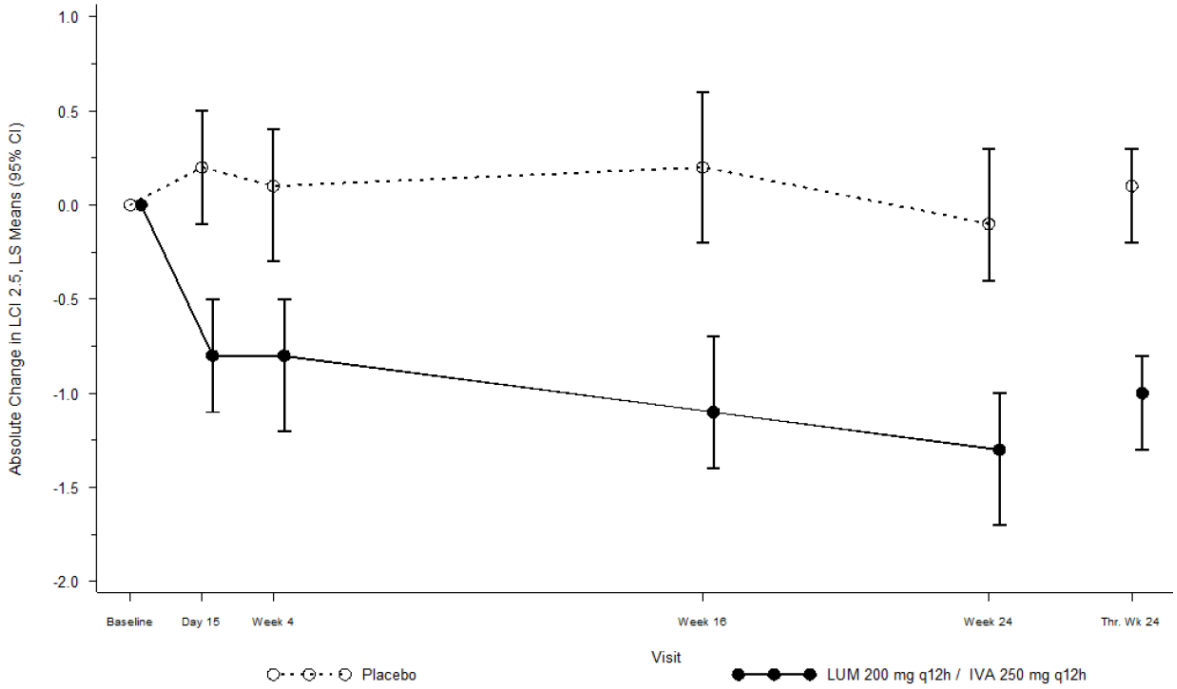
End point	Parameter	LSM change (SE)		L200/IVA vs. Placebo	
		Placebo (N = 101)	L200/IVA (N = 103)	LSMD (95% CI)[a]	*P* value
$LCI_{2.5}$	n	99	99	–1.09 (–1.43 to –0.75)	< 0.0001
	Baseline, mean (SD)	10.26 (2.24)	10.30 (2.36)		
	LSM (SE)	0.08 (0.13)	–1.01 (0.13)		
$LCI_{5.0}$	n	99	99	–0.44 (–0.57 to –0.31)	< 0.0001
	Baseline, mean (SD)	6.18 (0.92)	6.17 (0.96)		
	LSM (SE)	0.08 (0.05)	–0.36 (0.05)		

CI = confidence interval; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; LCI = lung clearance index; LSM = least squares mean; LSMD = least squares mean difference; SD = standard deviation; SE = standard error, vs. = versus.

[a] Mixed-effects model for repeated measures that included adjustment for weight (< 25 kg versus ≥ 25 kg), per cent predicted forced expiratory volume in one second at screening (< 90% versus ≥ 90%), and baseline value of the end point.

Source: Clinical study report.[7]

Figure 7: Absolute change from baseline in $LCI_{2.5}$ in Study 109



CI = confidence interval; IVA = ivacaftor; LCI = lung clearance index; LS = least squares; LUM = lumacaftor; q12h = every twelve hours.
Source: Clinical study report.[7]

Pulmonary Exacerbations

Patients 12 Years and Older

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 inconclusive, 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 L400/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 L400/IVA was associated with lower rates of pulmonary exacerbations requiring hospitalization and pulmonary exacerbations requiring IV antibiotic therapy (Figure 8). Hazard ratios for the previously noted end points demonstrated a favourable treatment for L400/IVA compared with placebo (Table 20). For all end points related to pulmonary exacerbations, the results demonstrated numerical or statistically significant differences in favour of L400/IVA.

Patients Aged Six Years to 11 Years

As shown in Figure 8, there was no statistically significant difference between the L200/IVA and placebo groups in the rate of any pulmonary exacerbations in Study 109 (rate ratio: 1.33 [95% CI, 0.70 to 2.53]). Table 20 summarizes the results for time-to-first pulmonary exacerbation, hospitalization for pulmonary exacerbation, and pulmonary exacerbations requiring IV antibiotic therapy. There were no statistical comparisons conducted for these end points in Study 109.

Table 20: Time-to-First Pulmonary Exacerbation in TRAFFIC and TRANSPORT

Time-to-First Pulmonary Exacerbation in TRAFFIC and TRANSPORT				
End Points	**TRAFFIC**		**TRANSPORT**	
	Placebo (N = 184)	**L400/IVA (N = 182)**	**Placebo (N = 187)**	**L400/IVA (N = 187)**
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	

Time-to-First Pulmonary Exacerbation in Study 109		
End points	**Placebo (N = 101)**	**L200/IVA (N = 103)**
Time-to-first Pulmonary Exacerbation		
Patients with event, n (%)	[redacted] (14.9)	[redacted] (19.4)
Event-free probability (95% CI)[b]	0.849 (0.761 to 0.906)	0.800 (0.707 to 0.866)
P value	NA	NA
Time-to-First Hospitalization for Pulmonary Exacerbation		
Patients with event, n (%)	[redacted]	[redacted]
Event-free probability (95% CI)[b]	[redacted]	[redacted]
P value	NA	NA
Time-to-First Pulmonary Exacerbations Requiring IV Antibiotic Therapy		
Patients with event, n (%)	[redacted]	[redacted]
Event-free probability (95% CI)[b]	[redacted]	[redacted]
P value	NA	NA

CI = confidence interval; IV = intravenous; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; L400/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; NA = not applicable; NR = not reported.

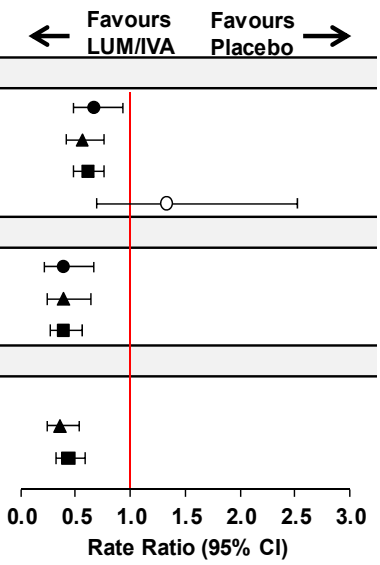
[a] Hazard ratio and *P* value were calculated using a Cox proportional-hazard regression analysis with adjustment for sex, age group (< 18 versus ≥ 18 years), and per cent predicted forced expiratory volume in one second at screening (< 70% versus ≥ 70%).[1,2]

[b] Kaplan–Meier methods to estimate cumulative exacerbation-free survival rates by treatment.

Source: Clinical study reports.[1,2,7]

Figure 8: Risk of Pulmonary Exacerbations from TRAFFIC, TRANSPORT, and Study 109

Age group	Study	Events (event rate/year) Placebo	Events (event rate/year) LUM/IVA	LUM/IVA vs. Placebo Rate Ratio (95% CI)	P value
Any pulmonary exacerbation					
≥12 Years	TRAFFIC	112 (1.07)	73 (0.71)	0.66 (0.47 to 0.93)	0.0169[a]
≥12 Years	TRANSPORT	139 (1.18)	79 (0.67)	0.57 (0.42 to 0.76)	0.0002[a]
≥12 Years	Pooled	251 (1.14)	152 (0.70)	0.61 (0.49 to 0.76)	<0.0001
6 to 11 Years	Study 109	18 (0.40)	24 (0.54)	1.33 (0.70 to 2.52)	0.3858
Pulmonary exacerbation requiring hospitalization					
≥12 Years	TRAFFIC	46 (0.36)	17 (0.14)	0.38 (0.22 to 0.67)	0.0008
≥12 Years	TRANSPORT	59 (0.46)	23 (0.18)	0.39 (0.24 to 0.64)	0.0002
≥12 Years	Pooled	105 (0.45)	40 (0.17)	0.39 (0.26 to 0.56)	<0.0001
Pulmonary exacerbation requiring IV antibiotics					
≥12 Years	TRAFFIC	62 (NA)	33 (NA)	No estimate	0.0050
≥12 Years	TRANSPORT	87 (0.64)	31 (0.23)	0.36 (0.24 to 0.54)	<0.0001
≥12 Years	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; NA = not applicable; vs. = versus.

Note: Regression analysis for a negative binomial distribution with sex (male versus female), age group at baseline (< 18 versus ≥ 18 years), and per cent predicted forced expiratory volume in one second ($ppFEV_1$) at screening (< 70% versus ≥ 70%) as covariates with the logarithm of time on study as the offset in TRAFFIC and TRANSPORT.[1,2] Regression analysis for a negative binomial distribution with weight (< 25 kg versus ≥ 25 kg) and $ppFEV_1$ severity at screening (< 90% versus ≥ 90%) as covariates in Study 109.

This figure shows rate ratios for LUM/IVA versus placebo for pulmonary exacerbations in TRAFFIC (●), TRANSPORT (▲), a pooled analysis of TRAFFIC and TRANSPORT conducted by the manufacturer (■), and Study 109 (O).

[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.

Source: Data from clinical study reports.[1,2,7]

Body Mass Index

Patients 12 Years and Older

Change from baseline in BMI was a key secondary end point of the included studies and, therefore, was part of 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 9 and Table 21). In TRANSPORT, treatment with L400/IVA was associated with a statistically significant improvement in BMI (0.36 kg/m^2; 95% CI, 0.17 to 0.54) compared with placebo. In contrast, L400/IVA failed to demonstrate a statistically significant difference for this end point in TRAFFIC (stopping the statistical testing hierarchy). The difference between L400/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 12 to less than 18 years of age and those who were over 18 years of age. In Study 112, there was no statistically significant

difference between L400/IVA and placebo for change from baseline in BMI (0.2 kg/m^2 [95% CI, −0.3 to 0.6]).

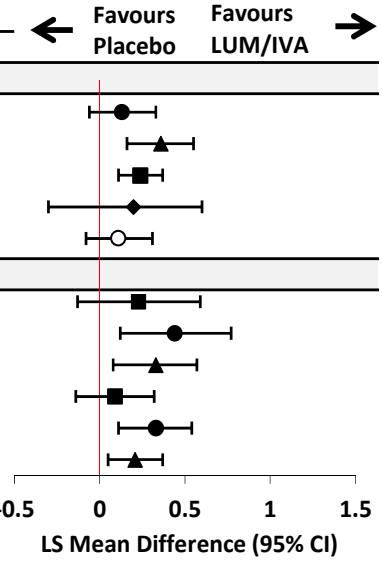
Treatment with L400/IVA was associated with a statistically significant improvement in BMI z score compared with placebo in TRANSPORT (0.222; 95% CI, 0.096 to 0.347) and in the pooled analysis ([redacted])(Figure 10 and Table 22). There was no statistically significant difference in TRAFFIC (0.078 [95% CI, −0.062 to 0.218]).

Patients Aged Six Years to 11 Years

Change from baseline in BMI was a key secondary end point of Study 109. There were no statistically significant differences between L200/IVA and placebo for change from baseline in BMI or BMI z scores. At 24 weeks, mean BMI z scores had increased in both the L200/IVA group (0.08 [SE: 0.04]) and the placebo group (0.05 [SE: 0.04]) of Study 109. A larger increase was reported in Study 11B, where L200/IVA-treated patients showed an increase of 0.15 (0.04) at week 24 (Table 40).The comparisons in both studies were not adjusted for multiplicity and should be interpreted accordingly.

Figure 9: Change from Baseline in Body Mass Index from TRAFFIC, TRANSPORT, Study 112, and Study 109

Age Group	Study	LS mean change (SE) Placebo	LS mean change (SE) LUM/IVA	LUM/IVA vs. Placebo LSMD (95% CI)	LUM/IVA vs. Placebo P value
Full Analysis					
≥12 Years	TRAFFIC	0.19 (0.070)	0.32 (0.071)	0.13 (−0.07, 0.32)	0.1938
≥12 Years	TRANSPORT	0.07 (0.066)	0.43 (0.066)	0.36 (0.17, 0.54)	0.0001
≥12 Years	Pooled	0.13 (0.048)	0.37 (0.048)	0.24 (0.11, 0.37)	0.0004
≥12 Years	Study 112	0.3 (0.16)	0.5 (0.16)	0.2 (−0.3, 0.6)	0.3961
6 to 11 years	Study 109	0.27 (0.07)	0.38 (0.07)	0.11 (−0.08, 0.31)	0.2522
Subgroups					
12 to 18 years	TRAFFIC	0.41 (0.128)	0.64 (0.130)	0.23 (−0.13, 0.59)	0.2085
12 to 18 years	TRANSPORT	0.17 (0.118)	0.61 (0.115)	0.44 (0.12, 0.77)	0.0078
12 to 18 years	Pooled	0.30 (0.088)	0.63 (0.087)	0.33 (0.08, 0.57)	0.0088
≥18 years	TRAFFIC	0.11 (0.081)	0.20 (0.083)	0.09 (−0.14, 0.32)	0.4344
≥18 years	TRANSPORT	0.03 (0.077)	0.35 (0.078)	0.33 (0.11, 0.54)	0.0027
≥18 years	Pooled	0.07 (0.056)	0.28 (0.057)	0.21 (0.05, 0.37)	0.0081



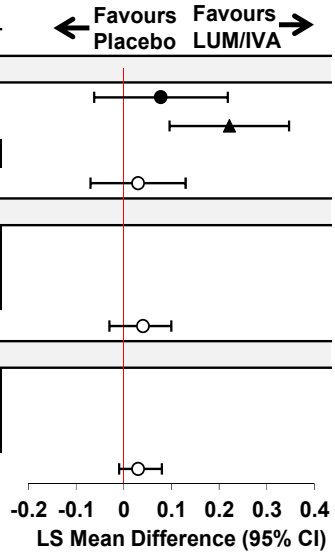
BMI = body mass index; CI = confidence interval; LS = least squares; LSMD = least squares mean difference; LUM/IVA = lumacaftor/ivacaftor; SE = standard error; vs. = versus.

Note: Mixed-effects model for repeated measures included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 versus ≥ 18 years), per cent predicted forced expiratory volume in one second severity at screening (< 70% versus ≥ 70%), and the baseline value for the end point of interest.[1,2]

This figure shows absolute change from baseline in BMI for LUM 400 mg every 12 hours/IVA 250 mg once every 12 hours versus placebo for TRAFFIC (●), TRANSPORT (▲), the pooled analysis conducted by the manufacturer (■), Study 112 (◆), and for LUM 200 mg once daily/IVA 250 mg once every 12 hours versus placebo for Study 109 (O).

Figure 10: Change from Baseline in Z Scores for Body Mass Index, Body Weight, and Height from TRAFFIC, TRANSPORT, and Study 109

Age group	Study	LS mean change (SE) Placebo	LS mean change (SE) LUM/IVA	LUM/IVA vs. Placebo LSMD (95% CI)	LUM/IVA vs. Placebo P value
BMI z-score					
≥12 Years	TRAFFIC	0.015 (0.049)	0.093 (0.054)	0.078 (−0.062, 0.218)	0.2713
≥12 Years	TRANSPORT	−0.067 (0.047)	0.154 (0.045)	0.222 (0.096, 0.347)	0.0006
≥12 Years	Pooled	[redacted]			
6 to 11 Years	Study 109	0.05 (0.04)	0.08 (0.04)	0.03 (−0.07, 0.13)	0.5648
Body weight z-score					
≥12 Years	TRAFFIC	[redacted]			
≥12 Years	TRANSPORT				
≥12 Years	Pooled				
6 to 11 Years	Study 109	0.02 (0.02)	0.06 (0.02)	0.04 (−0.03, 0.10)	0.2789
Height z-score					
≥12 Years	TRAFFIC	[redacted]			
≥12 Years	TRANSPORT				
≥12 Years	Pooled				
6 to 11 Years	Study 109	0.00 (0.02)	0.03 (0.02)	0.03 (−0.01, 0.08)	0.1505



BMI = body mass index; CI = confidence interval; LS = least squares; LSMD = least squares mean difference; LUM/IVA = lumacaftor/ivacaftor; SE = standard error; vs. = versus.

Note: Mixed-effects model for repeated measures (MMRM) included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 versus ≥ 18 years), per cent predicted forced expiratory volume in one second ($ppFEV_1$) severity at screening (< 70% versus ≥ 70%), and the baseline value for the end point of interest for TRAFFIC and TRANSPORT.[1,2] MMRM that included adjustment for weight (< 25 kg versus ≥ 25 kg), $ppFEV_1$ at screening (< 90% versus ≥ 90%), and baseline value of the end point in Study 109.[7]

This 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 (■).

Body Weight and Height

Patients 12 Years and Older

Changes in body weight and height were secondary end points in TRAFFIC and TRANSPORT. 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 inconclusive due to the risk of type I error. Similarly, the statistical testing for the pooled analyses for change from baseline in weight and height (including the z score analysis) were conducted without adjusted for multiplicity and should be interpreted with caution.

Neither the TRAFFIC nor TRANSPORT studies demonstrated a statistically significant difference for L400/IVA compared with placebo for changes in height (Table 21) or height z score (Figure 10) 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 L400/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, L400/IVA failed to demonstrate a statistically significant difference for these end points in TRAFFIC. The pooled analysis demonstrated an improvement statistically significant difference in favour of L400/IVA for change from baseline in body weight (0.62 kg; 95% CI, [redacted]) and body weight z score ([redacted]) (Table 22).

Patients Aged Six Years to 11 Years

There were no statistically significant differences between L200/IVA and placebo in Study 109 with respect to absolute change from baseline in weight, weight z score, height or height z score (Table 21). At 24 weeks, weight z scores had increased in both the L200/IVA group (0.02 [SD: 0.02]) and placebo group (0.06 [SD: 0.02]) in Study 109. Similar to BMI, a larger increase in weight z score was reported in Study 11B, where L200/IVA-treated patients showed an increase of 0.13 (SD: 0.03) from baseline at week 24 (Table 40). The increase in height z scores was similar in L200/IVA-treated patients in studies 109 and 11B (0.03 in both).The comparisons in both studies were not adjusted for multiplicity and should be interpreted accordingly.

Table 21: Absolute Changes from Baseline in BMI, Weight, and Height at week 24 from TRAFFIC, TRANSPORT, Study 112, and Study 109

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, mean (SD)	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, mean (SD)	21.02 (2.887)	21.32 (2.894)		
		LS mean (SE)	0.07 (0.066)	0.43 (0.066)		
	Pooled (TRAFFIC and TRANSPORT)	n	367	356	0.24 (0.11 to 0.37)	0.0004
		Baseline, mean (SD)	21.02 (2.918)	21.50 (3.034)		
		LS mean (SE)	0.13 (0.048)	0.37 (0.048)		
	Study 112	n	33	30	0.2 (−0.3 to 0.6)	0.3961
		Baseline, mean (SD)	0.3 (0.70)	0.6 (1.05)		
		LS mean (SE)	0.3 (0.16)	0.5 (0.16)		
	Study 109	n	97	98	0.11 (−0.08 to 0.31)	0.2522
		Baseline, mean (SD)	16.55 (1.96)	16.38 (1.66)		
		LS mean (SE)	0.27 (0.07)	0.38 (0.07)		
Weight (kg)	TRAFFIC	n	184	176	0.30 (−0.26 to 0.86)	0.2992
		Baseline, mean (SD)	[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, mean (SD)	[redacted]	[redacted]		
		LS mean (SE)	0.44 (0.187)	1.38 (0.187)		
	Pooled (TRAFFIC and TRANSPORT)	n	371	369	0.62 ([redacted])	0.0013
		Baseline, mean (SD)	[redacted]	[redacted]		
		LS mean (SE)	0.69 (0.138)	1.31 (0.139)		
	Study 109	n	97	98	[redacted]	[redacted]
		Baseline, mean (SD)	[redacted]	[redacted]		
		LS mean (SE)	1.7 (0.2)	2.0 (0.1)		
Height[a] (cm)	TRAFFIC	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline, mean (SD)	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	TRANSPORT	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline, mean (SD)	[redacted]	[redacted]		

End point	Study	Parameter	Placebo	LUM/IVA	LUM/IVA vs. Placebo	
					LSMD (95% CI)[b]	*P* value
		LS mean (SE)	[redacted]	[redacted]		
	Pooled (TRAFFIC and TRANSPORT)	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline, mean (SD)	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	Study 109	n	97	98	[redacted]	[redacted]
		Baseline, mean (SD)	[redacted]	[redacted]		
		LS mean (SE)	2.6 (0.1)	2.9 (0.1)		

BMI = body mass index; CI = confidence interval; LS = least squares; LSMD = least squares mean difference; LUM/IVA = lumacaftor/ivacaftor; SD = standard deviation; SE = standard error; vs. = versus.

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

[b] Mixed-effects model for repeated measures (MMRM) included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 versus ≥ 18 years), per cent predicted forced expiratory volume in one second ($ppFEV_1$) severity at screening (< 70% versus ≥ 70%), and the baseline value for the end point of interest in TRAFFIC and TRANSPORT.[1,2] MMRM that included adjustment for weight (< 25 kg versus ≥ 25 kg), $ppFEV_1$ at screening (< 90% versus ≥ 90%), and baseline value of the end point in Study 109.[7]

Source: Clinical study reports[1,2,6-8] and Common Technical Document.[5]

Table 22: Absolute Change from Baseline in Z Scores for BMI, Weight, and Height at Week 24 from TRAFFIC, TRANSPORT, and Study 109

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, mean (SD)	−0.590 (0.976)	−0.365 (0.814)		
		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	−0.500 (0.890)	−0.333 (0.901)		
		LS mean (SE)	−0.067 (0.047)	0.154 (0.045)		
	Pooled (TRAFFIC and TRANSPORT)	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline, mean (SD)	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	Study 109	n	97	98	0.03 (−0.07 to 0.13)	0.5648
		Baseline, mean (SD)	−0.14 (0.88)	−0.14 (0.84)		
		LS mean (SE)	0.05 (0.04)	0.08 (0.04)		
Weight z score[a]	TRAFFIC	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline, mean (SD)	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	TRANSPORT	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	Pooled (TRAFFIC and TRANSPORT)	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline, mean (SD)	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	Study 109	n	97	98	0.04 (–0.03 to 0.10)	0.2789
		Baseline, mean (SD)	−0.21 (0.76)	−0.21 (0.82)		
		LS mean (SE)	0.02 (0.02)	0.06 (0.02)		
Height z score[a]	TRAFFIC	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline, mean (SD)	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	TRANSPORT	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline, mean (SD)	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	Pooled (TRAFFIC and TRANSPORT)	n	[redacted]	[redacted]	[redacted]	[redacted]
		Baseline, mean (SD)	[redacted]	[redacted]		
		LS mean (SE)	[redacted]	[redacted]		
	Study 109	n	97	98	0.03 (−0.01 to 0.08)	0.1505
		Baseline, mean (SD)	−0.16 (0.76)	−0.11 (0.97)		
		LS mean (SE)	0.00 (0.02)	0.03 (0.02)		

BMI = body mass index; CI = confidence interval; LS = least squares; LSMD = least squares mean difference; LUM/IVA = lumacaftor/ivacaftor; SD = standard deviation; SE = standard error; vs. = versus.

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

[b] Mixed-effects model for repeated measures (MMRM) included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 versus ≥ 18 years), per cent predicted forced expiratory volume in one second ($ppFEV_1$) severity at screening (< 70% versus ≥ 70%), and the baseline value for the end point of interest in TRAFFIC and TRANSPORT.[1,2] MMRM that included adjustment for weight (< 25 kg versus ≥ 25 kg), $ppFEV_1$ at screening (< 90% versus ≥ 90%), and baseline value of the end point in Study 109.[7]

Source: Clinical study reports[1,2,6-8] and Common Technical Document.[5]

Symptoms

Cystic Fibrosis Questionnaire – Revised

Patients 12 Years and Older

Differences in change from baseline the respiratory domain of the CFQ-R 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 inconclusive. Similarly, the statistical testing for the pooled analysis was conducted without adjusted for multiplicity and should be interpreted in light of the risk of type I error.

There was no statistically significant difference between L400/IVA and placebo for change from baseline to week 24 in the CFQ-R respiratory domain (Table 23) in the individual TRAFFIC and TRANSPORT studies or in the pooled analysis. Based on the hierarchical testing procedure, the testing hierarchy stopped at this end point in the TRANSPORT study.

There was no statistically significant difference between L400/IVA and placebo in Study 112 (LSMD: 5.0 [95% CI, −2.6 to 12.7]).

Patients Aged Six Years to 11 Years

As shown in Table 23, there was no statistically significant difference between L200/IVA and placebo for change from baseline to week 24 in the CFQ-R respiratory domain for either the patient or parent and caregiver versions (LSMD: 2.5 [95% CI, −0.1 to 5.1] and 2.6 [95% CI, −1.4 to 6.5], respectively) in Study 109. The comparison was not adjusted for multiplicity and should be interpreted accordingly.

Health-Related Quality of Life

EuroQol 5-Dimensions 3-Levels Survey

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 inconclusive, and the results should be interpreted with caution.

There was no statistically significant difference between L400/IVA and placebo for change from baseline to week 24 in the EQ-5D-3L utility scores or EQ-5D VAS (Table 23). For the EQ-5D-3L VAS, there was a numerical difference favouring L400/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 L400/IVA versus placebo at 24 weeks.[5]

Table 23: Absolute Change from Baseline in CFQ-R Respiratory Domain and EQ-5D-3L from TRAFFIC, TRANSPORT, Study 112, and Study 109

End point	Study	Parameter	LS mean change (SE)		LUM/IVA vs. 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, mean (SD)	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, mean (SD)	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, mean (SD)	68.78 (17.328)	68.31 (17.998)		
		LSM (SE)	1.88 (0.818)	4.10 (0.834)		
	Study 112	n	33	30	6.2 (–1.8 to 14.1)	0.1257
		Baseline, mean (SD)	66.0 (19.39)	69.9 (16.78)		
		LSM (SE)	6.1 (2.80)	0.1 (3.00)		
	Study 109 (Patients)	n	78	76	2.5 (−0.1 to 5.1)	0.0628
		Baseline, mean (SD)	77.1 (15.5)	78.7 (14.0)		
		LSM (SE)	3.0 (1.0)	5.5 (1.0)		
	Study 109 (Parents and Caregivers)	n	96	98	2.6 (−1.4 to 6.5)	0.2038
		Baseline, mean (SD)	82.2 (15.3)	82.1 (14.9)		
		LSM (SE)	1.0 (1.5)	3.6 (1.5)		
EQ-5D-3L (Utility score)	TRAFFIC	n	179	170	0.0095 (−0.0109 to 0.0298)	0.3613
		Baseline, mean (SD)	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, mean (SD)	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, mean (SD)	75.4 (16.42)	73.7 (17.30)		
		LSM (SE)	1.4 (1.03)	2.8 (1.04)		
	TRANSPORT	n	182	177	3.3 (0.4 to 6.2)	0.0262
		Baseline, mean (SD)	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-Dimension 3-Levels; LS = least squares; LSM = least squares mean; LSMD = least squares mean difference; LUM/IVA = lumacaftor/ivacaftor; SD = standard deviation; SE = standard error; VAS = visual analogue score; vs. = versus.

[a] Mixed-effects model for repeated measures (MMRM) included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 years versus ≥ 18 years), per cent predicted forced expiratory volume in one second ($ppFEV_1$) severity at screening (< 70% versus ≥ 70%), and the baseline value for the end point of interest in TRAFFIC and TRANSPORT.[1,2] MMRM that included adjustment for weight (< 25 kg versus ≥ 25 kg), $ppFEV_1$ at screening (< 90% versus ≥ 90%), and baseline value of the end point in Study 109.[7]

Source: Clinical study reports[1,2,7] and Common Technical Document section 5.3.5.3.[5]

Harms

Only those harms identified in the review protocol are subsequently reported. A summary of AEs from the included studies is provided in Table 24.

Patients 12 Years and Older

In accordance with the manufacturer's safety analysis plan,[4] this section of the report summarizes pooled AEs from TRAFFIC and TRANSPORT. The pooled data set consists of patients who received L400/IVA (n = 369); patients who received L600/IVA (n = 369), and patients who received placebo (n = 370). The CADTH systematic review is focused only on the Health Canada–approved dosage of LUM/IVA; therefore, data for the L600/IVA dosage regimen are not summarized.

The proportion of patients who experienced at least one AE was similar in the L400/IVA groups of all studies (range: 88.2% to 95.1%) and similar in the placebo groups (95.9% to 97.2%). In Study 112, the proportion of patients who experienced an AE was lower in the L400/IVA group than in the placebo group (88.2% versus 97.2%). In the TRAFFIC and TRANSPORT studies, the proportion of patients who experienced at least one SAE was lower in the L400/IVA group than in the placebo group (28.6% versus 17.3%, respectively). WDAEs were more frequent in the L400/IVA group than in the placebo groups in TRAFFIC and TRANSPORT (4.6% versus 1.6%, respectively), The proportion of patients with AEs leading to treatment interruption were similar between the L400/IVA and placebo groups in TRAFFIC and TRANSPORT (6.0% versus 6.8%, respectively), but were greater in the L400/IVA group of Study 112 (5.9% versus 0%).There were no deaths reported in TRAFFIC, TRANSPORT, or Study 112.[4,8]

Patients Aged Six Years to 11 Years

The proportion of patients who experienced at least one AE in the L200/IVA groups was similar in the two studies (94.8% to 95.1% in Study 11B and Study 109, respectively) and was similar in the placebo group (97.0%). In Study 109, the proportion of patients who experienced at least one SAE was 12.6% in the L200/IVA group compared with 10.9% in the placebo group. The rate of SAEs was lower in Study 11B (6.9%). WDAEs were similar in the L200/IVA and placebo group of Study 109 (2.9% versus 2.0%, respectively). AEs leading to treatment interruption were more common with L200/IVA than with placebo in Study 109 (8.7% versus 3.0%, respectively).There were no deaths reported in either Study 11B or Study 109.[6,7]

Table 24: Summary of Adverse Events

Adverse Events, n (%)	≥ 12 years				6 Years to 11 Years		
	TRAFFIC and TRANSPORT		Study 112		Study 109		Study 11B
	Placebo (N = 370)	L400/IVA (N = 369)	Placebo (N = 36)	L400/IVA (N = 34)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Any AEs	355 (95.9)	351 (95.1)	35 (97.2)	30 (88.2)	98 (97.0)	98 (95.1)	55 (94.8)
AEs leading to discontinuation	6 (1.6)	17 (4.6)	0	2 (5.9)	2 (2.0)	3 (2.9)	2 (3.4)
AEs leading to interruption	25 (6.8)	22 (6.0)	0	1 (2.9)	3 (3.0)	9 (8.7)	6 (10.3)
Grade 3 or 4 AEs	59 (15.9)	45 (12.2)	9 (25.0)	15 (44.1)	8 (7.9)	3 (2.9)	4 (6.9)
SAEs	106 (28.6)	64 (17.3)	0	2 (5.9)	11 (10.9)	13 (12.6)	4 (6.9)
AEs leading to death	0	0	0	0	0	0	0

AE = adverse event; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; SAE = serious adverse event.

Sources: Common Technical Document section 2.7.4[4] and clinical study reports.[1,2,6-8]

Adverse Events

Table 25 provides a summary of the most frequently reported AEs in the included studies (i.e., those occurring in at least 5% patients in one of the treatment groups).

Patients 12 Years and Older

In TRAFFIC and TRANSPORT, the overall proportion of patients who experienced at least one AE was similar between the placebo groups (95.9%) and the L400/IVA groups (95.1%). The most commonly reported AEs in both the placebo and L400/IVA groups (respectively) were infective pulmonary exacerbations (49.2% versus 35.8%). AEs that were reported in ≥ 5% of patients in the L400/IVA group and occurred at a higher frequency than in 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%), increased blood creatine phosphokinase (7% versus 5%), and rash (7% versus 2%).[4] Consistent with efficacy data, there were fewer pulmonary exacerbations in the placebo group than in the L400/IVA group in TRAFFIC and TRANSPORT. In addition, fewer L400/IVA-treated patients reported cough, sputum increase, nasal congestion, or experienced a decrease on the pulmonary function test with L400/IVA compared with placebo.[4]

Patients Aged Six Years to 11 Years

The overall proportion of patients who experienced at least one AE was similar between the L200/IVA and placebo groups of Study 109 (95.2% with L200/IVA and 97.0% with placebo). Compared with the studies conducted in patients who were at least 12 years of age, infective pulmonary exacerbations occurred at a lower frequency in both the L200/IVA and placebo groups of Study 109 (12.6% versus 15.8%) and in Study 11B (20.7%). Cough was the most frequently AE in the studies conducted in patients aged six years to 11 years (44.7% and 46.5% with L200/IVA and placebo in Study 109 and 50.0% in Study 11B). In Study 109, AEs that occurred more frequently in L200/IVA-treated patients than placebo-treated patients were productive cough (17.5% versus 5.9%), nasal congestion (16.5% versus 7.9%), oropharyngeal pain (14.6% versus 9.9%), headache (12.6% versus 8.9%), increased sputum (10.7% versus 2.0%), upper abdominal pain (12.6% versus 6.9%), rhinorrhea (9.7% versus 5.0%), and rash (5.8% versus 1.0%).

Table 25: Adverse Events Reported for at Least Five Per Cent of Patients

Adverse Events, n (%)	≥ 12 years				6 Years to 11 Years		
	TRAFFIC and TRANSPORT		Study 112		Study 109		Study 11B
	Placebo (N = 370)	L400/IVA (N = 369)	Placebo (N = 36)	L400/IVA (N = 34)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Any AEs	355 (95.9)	351 (95.1)	35 (97.2)	30 (88.2)	98 (97.03)	98 (95.15)	55 (94.8)
Infective PEx of CF	182 (49.2)	132 (35.8)	12 (33.3)	12 (35.3)	18 (17.8)	20 (19.4)	12 (20.7)
Cough	148 (40.0)	104 (28.2)	8 (22.2)	5 (14.7)	47 (46.53)	46 (44.66)	29 (50.0)
Headache	58 (15.7)	58 (15.7)	2 (5.6)	0	9 (8.91)	13 (12.62)	12 (20.7)
Increased sputum	70 (18.9)	54 (14.6)	5 (13.9)	2 (5.9)	2 (1.98)	11 (10.68)	8 (13.8)
Dyspnea	29 (7.8)	48 (13.0)	3 (8.3)	1 (2.9)	NR	NR	NR
Hemoptysis	50 (13.5)	50 (13.6)	2 (5.6)	3 (8.8)	NR	NR	NR
Diarrhea	31 (8.4)	45 (12.2)	3 (8.3)	1 (2.9)	4 (3.96)	6 (5.83)	4 (6.9)
Nausea	28 (7.6)	46 (12.5)	5 (13.9)	3 (8.8)	9 (8.91)	10 (9.71)	6 (10.3)
Abnormal respiration	22 (5.9)	32 (8.7)	9 (25.0)	5 (14.7)	4 (3.96)	6 (5.83)	NR
Nasopharyngitis	40 (10.8)	48 (13.0)	3 (8.3)	3 (8.8)	8 (7.92)	5 (4.85)	NR
Oropharyngeal pain	30 (8.1)	24 (6.5)	4 (11.1)	1 (2.9)	10 (9.90)	15 (14.56)	3 (5.2)
Pyrexia	34 (9.2)	33 (8.9)	0	2 (5.9)	20 (19.80)	15 (14.56)	6 (10.3)
Fatigue	29 (7.8)	34 (9.2)	NR	NR	11 (10.89)	9 (8.74)	6 (10.3)
URTI	20 (5.4)	37 (10.0)	4 (11.1)	4 (11.8)	10 (9.90)	13 (12.62)	3 (5.2)
Abdominal pain	32 (8.6)	33 (8.9)	NR	NR	10 (9.90)	10 (9.71)	6 (10.3)
Abdominal discomfort	NR	NR	NR	NR	NR	NR	3 (5.2)
GERD	NR	NR	0	3 (8.8)	NR	NR	0
Nasal congestion	44 (11.9)	24 (6.5)	NR	NR	8 (7.92)	17 (16.50)	12 (20.7)
Viral URTI	25 (6.8)	23 (6.2)	2 (5.6)	1 (2.9)	8 (7.92)	5 (4.85)	3 (5.2)
Rhinitis	18 (4.9)	16 (4.3)	NR	NR	5 (4.95)	6 (5.83)	NR
Flatulence	11 (3.0)	24 (6.5)	NR	NR	NR	NR	NR
Increased blood CPK	20 (5.4)	27 (7.3)	1 (2.8)	2 (5.9)	NR	NR	NR
Rash	7 (1.9)	25 (6.8)	2 (5.6)	0	1 (0.99)	6 (5.83)	4 (6.9)
Sinusitis	19 (5.1)	16 (4.3)	2 (5.6)	0	NR	NR	3 (5.2)
Rhinorrhea	15 (4.1)	21 (5.7)	NR	NR	5 (4.95)	10 (9.71)	5 (8.6)
Vomiting	11 (3.0)	16 (4.3)	NR	NR	10 (9.90)	10 (9.71)	6 (10.3)
Influenza	8 (2.2)	19 (5.1)	NR	NR	6 (5.94)	4 (3.88)	NR
Upper abdominal pain	18 (4.9)	12 (3.3)	NR	NR	7 (6.93)	13 (12.62)	8 (13.8)
Constipation	21 (5.7)	14 (3.8)	2 (5.6)	0	8 (7.92)	5 (4.85)	5 (8.6)
Decrease on pulmonary function test	20 (5.4)	3 (0.8)	NR	NR	NR	NR	3 (5.2)
Decreased appetite	NR	NR	NR	NR	6 (5.94)	3 (2.91)	3 (5.2)
Otitis media	NR	NR	NR	NR	NR	NR	3 (5.2)
Pharyngitis streptococcal	NR	NR	NR	NR	NR	NR	3 (5.2)
ALT increased	NR	NR	NR	NR	9 (8.9)	8 (7.77)	7 (12.1)
Positive bacterial test	NR	NR	2 (5.6)	0	8 (7.92)	7 (6.80)	NR
Increased AST	NR	NR	NR	NR	7 (6.9)	6 (5.83)	4 (6.9)
Productive cough	NR	NR	2 (5.6)	1 (2.9)	6 (5.94)	18 (17.48)	NR
Rales	NR	NR	NR	NR	NR	NR	3 (5.2)
Dermatitis contact	NR	NR	NR	NR	NR	NR	3 (5.2)
Seasonal allergy	NR	NR	NR	NR	NR	NR	3 (5.2)

Adverse Events, n (%)	≥ 12 years				6 Years to 11 Years		
	TRAFFIC and TRANSPORT		Study 112		Study 109		Study 11B
	Placebo (N = 370)	L400/IVA (N = 369)	Placebo (N = 36)	L400/IVA (N = 34)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Increased viscosity of bronchial secretion	NR	NR	0	3 (8.8)	NR	NR	NR
Anxiety	NR	NR	0	2 (5.9)	NR	NR	NR
Distal intestinal obstruction syndrome	NR	NR	0	2 (5.9)	NR	NR	NR
Toothache	NR	NR	0	2 (5.9)	NR	NR	NR
Back pain	NR	NR	2 (5.6)	0	NR	NR	NR
Decreased blood iron	NR	NR	2 (5.6)	0	NR	NR	NR
Dermatitis allergic	NR	NR	2 (5.6)	0	NR	NR	NR
Positive fungal test	NR	NR	2 (5.6)	0	NR	NR	NR
Vulvovaginal candidiasis	NR	NR	3 (8.3)	0	NR	NR	NR

AE = adverse event; ALT = alanine transaminase; AST= aspartate transaminase; CF = cystic fibrosis; CPK = creatine phosphokinase; GERD = gastroesophageal reflux disease; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; NR = not reported; PEx = pulmonary exacerbation; URTI = upper respiratory tract infection.

Source: Common Technical Document[4] and clinical study reports.[1,2,6-8]

Serious Adverse Events

Table 26 provides a summary of the SAEs that were reported in the included studies.

Patients 12 Years and Older

In TRAFFIC and TRANSPORT, the proportion of patients who experienced at least one SAE was greater in the placebo group (28.6%) than in the L400/IVA group (17.3%). The most commonly reported SAE in any treatment group was infective pulmonary exacerbation of CF. There were more pulmonary exacerbations in the placebo group compared with the L400/IVA group (24.1% versus 11.1%, respectively). In Study 112, a greater proportion of L400/IVA-treated patients experienced at least one SAE compared with the placebo group (44.1% versus 25.0%). In contrast with TRAFFIC and TRANSPORT, the proportion of patients with serious pulmonary exacerbations was greater in the L400/IVA group than in the placebo group (23.5% versus 16.7%; though this was only a difference of two patients).

Patients Aged Six Years to 11 Years

In Study 109, the proportion of patients who experienced at least one SAE was 12.6% in the L200/IVA group and 10.9% in the placebo group (10.9%). The most commonly reported SAE in both the L200/IVA and placebo group was infective pulmonary exacerbation of CF (7.8% versus 5.0%, respectively). The proportion of patients who experienced at least one SAE was lower in Study 11B (6.9%), with serious infective pulmonary exacerbations reported for 3.5% of patients.

Table 26: Serious Adverse Events

Serious Adverse Events, n (%)	≥ 12 years				6 Years to 11 Years		
	TRAFFIC and TRANSPORT		Study 112		Study 109		Study 11B
	Placebo (N = 370)	L400/IVA (N = 369)	Placebo (N = 36)	L400/IVA (N = 34)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Any SAEs	106 (28.6)	64 (17.3)	9 (25.0)	15 (44.1)	11 (10.89)	13 (12.62)	4 (6.90)
Infections and Infestations							
Infective PEx of CF	89 (24.1)	41 (11.1)	6 (16.7)	8 (23.5)	5 (4.95)	8 (7.77)	2 (3.45)
Pneumonia	0	1 (0.3)	0	0	1 (0.99)	1 (0.97)	0
Influenza	2 (0.5)	0	0	0	0	0	0
Bronchitis	2 (0.5)	0	0	0	0	0	0
Bronchopulmonary aspergillosis allergic	0	0	0	0	0	1 (0.97)	0
Infection	0	0	0	1 (2.9)	0	0	0
LRT infection bacterial	0	0	0	1 (2.9)	0	0	0
Cytomegalovirus infection	0	0	1 (2.8)	0	0	0	0
Respiratory, Thoracic, and Mediastinal Disorders							
Hemoptysis	3 (0.8)	5 (1.4)	1 (2.8)	0	0	0	0
Cough	0	1 (0.3)	0	0	0	0	0
Dyspnea	0	0	0	1 (2.9)	0	0	0
Obstructive airways disorder	0	0	0	0	0	1 (0.97)	0
Gastrointestinal Disorders							
Distal intestinal obstruction syndrome	5 (1.4)	2 (0.5)	0	2 (5.9)	2 (1.98)	0	0
Constipation	2 (0.5)	1 (0.3)	0	0	1 (0.99)	0	0
Ileus	0	0	0	0	0	0	1 (1.72)
Inguinal hernia	0	0	0	1 (2.9)	0	0	0
Cardiac Disorders							
Tachycardia	0	0	0	1 (2.9)	0	0	0
General Disorders and Administration Site Conditions							
Fatigue	0	0	0	1 (2.9)	0	0	0
Drug interaction	0	0	0	0	0	1 (1.0)	0
Reproductive System and Breast Disorders							
Testicular torsion	0	0	0	1 (2.9)	0	0	0
Investigations							
Increased blood CPK	0	2 (0.5)	0	0	0	0	0
Lymphadenitis	0	0	0	0	1 (0.99)	0	0
Bacterial test positive	0	0	0	0	0	1 (0.97)	0
Increased ALT	0	0	0	0	1 (0.99)	0	1 (1.72)
Increased AST	0	0	0	0	1 (0.99)	0	1 (1.72)
Increased transaminases	0	0	0	0	1 (0.99)	0	0
Renal and Urinary Disorders							
Nephrolithiasis	2 (0.5)	1 (0.3)	0	0	0	0	0
Vascular Disorders							
Deep vein thrombosis	2 (0.5)	0	0	0	0	0	0
Poor venous access	0	0	0	0	0	1 (0.97)	0

Serious Adverse Events, n (%)	≥ 12 years				6 Years to 11 Years		
	TRAFFIC and TRANSPORT		Study 112		Study 109		Study 11B
	Placebo (N = 370)	L400/IVA (N = 369)	Placebo (N = 36)	L400/IVA (N = 34)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Injury, Poisoning, Procedural Complications							
Procedural anxiety	0	0	0	0	0	1 (0.97)	0
Lower limb fracture	0	0	1 (2.8)	0	0	0	0

ALT = alanine transaminase; AST= aspartate transaminase; CF = cystic fibrosis; CPK = creatine phosphokinase; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; LRT = lower respiratory tract; PEx = pulmonary exacerbation; SAEs = serious adverse events.

Source: Common Technical Document[4] and clinical study reports.[1,2,6-8]

Withdrawals Due to Adverse Events

Table 27 provides a summary of the WDAEs that were reported in the included studies.

Patients 12 Years and Older

In TRAFFIC and TRANSPORT, WDAEs were more common in the L400/IVA group than in the placebo group (4.6% versus 1.6%). An increase in blood creatine phosphokinase resulted in the discontinuation of four L400/IVA patients compared with none in the placebo groups. Hemoptysis was the most commonly reported AE that resulted in patients discontinuing treatment (two patients in the placebo group and three patients in the L400/IVA group). The other AEs that resulted in the discontinuation of more than one patient were bronchospasm, dyspnea, pulmonary exacerbation, and rash.[4] There were no WDAEs reported in Study 112.[8]

Patients Six Years to 11 Years

In Study 109, the proportion of patients who withdrew as a result of AEs was similar in the L200/IVA and placebo groups (2.9% versus 2.0%, respectively). A similar proportion withdrew due to AEs in Study 11B (3.4%). These events were primarily attributed to increases in liver enzymes.

Table 27: Withdrawals Due to Adverse Events

Withdrawals Due to Adverse Events, n (%)	≥ 12 years				6 Years to 11 Years		
	TRAFFIC and TRANSPORT		Study 112		Study 109		Study 11B
	Placebo (N = 370)	L400/IVA (N = 369)	Placebo (N = 36)	L400/IVA (N = 34)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Any WDAEs	6 (1.6)	17 (4.6)	0	2 (5.4)	2 (2.0)	3 (2.9)	2 (3.4)
Respiratory, Thoracic, and Mediastinal Disorders							
Hemoptysis	2 (0.5)	3 (0.8)	0	0	0	0	0
Abnormal respiration	0	0	0	0	0	1 (1.0)	0
Investigations							
Increased blood CPK	0	4 (1.1)	0	0	0	0	0
Increased ALT	0	0	0	0	1 (1.0)	1 (1.0)	1 (1.7)
Increased AST	0	0	0	0	1 (1.0)	1 (1.0)	1 (1.7)
Increased transaminases	0	0	0	0	1 (1.0)	1 (1.0)	0

Withdrawals Due to Adverse Events, n (%)	≥ 12 years				6 Years to 11 Years		
	TRAFFIC and TRANSPORT		Study 112		Study 109		Study 11B
	Placebo (N = 370)	L400/IVA (N = 369)	Placebo (N = 36)	L400/IVA (N = 34)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Decreased FEV_1	0	1 (0.3)	0	0	0	0	0
Decrease on pulmonary function test	0	1 (0.3)	0	0	0	0	0
Increased blood ALP	1 (0.3)	0	0	0	0	0	0
Gastrointestinal Disorders							
Nausea	0	1 (0.3)	0	1 (2.9)	0	0	0
Frequent bowel movements	0	0	0	1 (2.9)	0	0	0
GERD	0	0	0	1 (2.9)	0	0	0
Infections and Infestations							
Infective PEx of CF	0	2 (0.5)	0	1 (2.9)	0	0	0
Metabolism and Nutrition Disorders							
Decreased appetite	0	0	0	1 (2.9)	0	0	0
Nervous System Disorders							
Hepatic encephalopathy	0	1 (0.3)	0	0	0	0	0
Restless legs syndrome	0	0	0	1 (2.9)	0	0	0
Sinus headache	0	0	0	1 (2.9)	0	0	0
Skin and Subcutaneous Tissue Disorders							
Rash	0	1 (0.3)	0	0	0	0	0
Urticaria	0	0	0	0	0	0	1 (1.7)
Acne	1 (0.3)	0	0	0	0	0	0
Blood and Lymphatic System Disorders							
Thrombocytosis	0	1 (0.3)	0	0	0	0	0
Immune System Disorders							
Drug hypersensitivity	0	1 (0.3)	0	0	0	0	0
Myalgia	0	1 (0.3)	0	0	0	0	0
Neoplasms Benign, Malignant, and Unspecified							
Renal cancer	1 (0.3)	0	0	0	0	0	0
Psychiatric Disorders							
Bradyphrenia	1 (0.3)	0	0	0	0	0	0

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; CF = cystic fibrosis; CPK = creatine phosphokinase; FEV_1 = forced expiratory volume in one second; GERD = gastroesophageal reflux disease; PEx = pulmonary exacerbation; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; WDAE = withdrawals due to adverse event.

Source: Common Technical Document[4] and clinical study reports.[1,2,6-8]

Notable Harms

The manufacturer identified respiratory symptoms, reactive airways, and elevated transaminases as AEs of special interest in its analysis of safety data from TRAFFIC and TRANSPORT.[4] In both Study 109 and Study 11B, elevated transaminases, respiratory symptoms, and respiratory events (i.e., events of respiratory symptoms and reactive airway) were categorized as AEs of special interest. In consultation with a clinical expert, CADTH has included the respiratory AEs, hepatic AEs, and ophthalmic AEs as additional harms of interest.[6,7] Hepatic AEs are summarized in Table 28 and respiratory AEs are summarized in Table 29.

Hepatic Adverse Events

Patients 12 Years and Older

In the TRAFFIC AND TRANSPORT studies, the proportion of patients who experienced at least one hepatic AE was similar in the L400/IVA group (6.0%) and the placebo group (5.4%). Elevated transaminases were reported in a slightly greater proportion of L400/IVA-treated patients than in 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 L400/IVA group and none in the placebo group.

Patients Aged Six Years to 11 Years

In Study 109, elevated transaminases were reported in a similar proportion of L200/IVA-treated patients compared with placebo-treated patients (9.7% versus 9.9%). The proportion of patients with elevated transaminases was 12.1% in Study 11B. A separate analysis was not provided for liver-related AEs in studies 109 or 11B.

Table 28: Hepatic Adverse Events

Hepatic Adverse Events, n (%)	≥ 12 years		6 Years to 11 Years		
	TRAFFIC and TRANSPORT		Study 109		Study 11B
	Placebo (N = 370)	L400/IVA (N = 369)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Any liver-related AEs	20 (5.4)	22 (6.0)	Not reported as an AESI		
Elevated transaminases	17 (4.6)	20 (5.4)	10 (9.9)	10 (9.7)	7 (12.1)
Increased alanine aminotransferase	9 (2.4)	8 (2.2)	9 (8.9)	8 (7.8)	7 (12.1)
Increased aspartate aminotransferase	8 (2.2)	9 (2.4)	7 (6.9)	6 (5.8)	4 (6.9)
Increased hepatic enzyme	0	4 (1.1)	0	0	0
Abnormal liver function test	6 (1.6)	3 (0.8)	0	0	0
Increased transaminases	1 (0.3)	2 (0.5)	1 (1.0)	2 (1.9)	0
Any other hepatobiliary disorder AEs	3 (0.8)	3 (0.8)	Not reported as an AESI		
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; AESI = adverse event of special interest; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours.

Source: Common Technical Document[4] and clinical study reports.[1,2,6-8]

Respiratory Adverse Events

Patients 12 Years and Older

TRAFFIC and TRANSPORT included two categories of respiratory AEs of special interest: respiratory symptoms and reactive airways. These categories were established based on observations from the phase II clinical trials where treatment with LUM appeared to be associated with an increased risk of respiratory AEs during the treatment-initiation period. A greater proportion of L400/IVA-treated patients (25.7%) had at least one respiratory AE compared with those who were treated with placebo (17.0%). This difference was primarily attributable to the greater proportion of L400/IVA-treated patients (22.0%) who experienced AEs related to respiratory symptoms compared with those in the placebo-treated group (13.8%). The proportion of reactive airway AEs was similar in the L400/IVA group (6.5%) and the placebo group (5.4%), with a difference of only four patients.[4] Nearly all respiratory AEs were mild or moderate in severity.[24]

Of the 81 L400/IVA-treated patients who experienced at least one AE related to respiratory symptoms, 80.2% (n = 65) experienced the event during the first week of treatment (Table 30). The occurrence of AEs was sharply reduced after the first week and the manufacturer reported that there was no difference between the L400/IVA and placebo groups after the first week. The median time to onset of respiratory symptom AEs was two days in the LUM/IVA group and 43 days in the placebo group. The mean duration of the respiratory AEs was 18.5 days in the L400/IVA group and 12.9 days in the placebo group.

The manufacturer conducted subgroup analyses to explore the occurrence of the respiratory AEs based on $ppFEV_1$ at screening (< 70% or ≥ 70%) and at baseline (< 40% or ≥ 40%). In both analyses, dyspnea was more commonly reported for patients with poorer lung function (Table 42). In the L400/IVA groups, there was approximately a twofold increase in dyspnea in 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.

Patients Aged Six Years to 11 Years

In studies 109 and 11B, respiratory symptoms and respiratory events (a composite of respiratory symptoms and reactive airway events) were specified as AE of special interest. The proportion of patients with any respiratory symptom AEs was similar in the L200/IVA group (10.7%) and the placebo group (8.9%).[7] The proportion was lower in Study 11B with 3.4% of patients reporting respiratory symptom AEs.[6] Respiratory events were more commonly reported in the L200/IVA group than in the placebo group in Study 109 (18.4% versus 12.9%). The proportion of patients with respiratory events was lower in Study 11B with 6.9%.[6] All of the events were mild or moderate in severity, though one L200/IVA-treated patient discontinued treatment as a result of these events in Study 109.[7]

In Study 109, the median time to onset for both respiratory symptoms and respiratory events was 17.0 days in the L200/IVA group and 10.0 days in placebo group (mean [SD] were 44.5 [51] days and 51.4 [66] days).The median duration of the events was greater in the L200/IVA group (8.5 days) compared with the placebo group (3.0 days).[7] In Study 11B, the median time to onset was considerably longer for both respiratory symptoms (50.5 days) and respiratory events (42.0 days). In addition, the median duration of events was only one day for both respiratory symptoms and respiratory events.

Table 29: Respiratory Adverse Events

Respiratory Adverse Events, n (%)	≥ 12 years				6 Years to 11 Years		
	TRAFFIC and TRANSPORT		Study 112		Study 109		Study 11B
	Placebo (N = 370)	L400/IVA (N = 369)	Placebo (N = 36)	L400/IVA (N = 34)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Respiratory Symptoms							
Any AESI of respiratory symptoms	51 (13.8)	81 (22.0)	Not reported as an AESI		9 (8.9)	11 (10.7)	2 (3.4)
Chest discomfort	5 (1.4)	7 (1.9)			1 (1.0)	0	0
Dyspnea	29 (7.8)	48 (13.0)			5 (5.0)	5 (4.9)	1 (1.7)
Abnormal respiration	22 (5.9)	32 (8.7)			4 (4.0)	6 (5.8)	1 (1.7)
Leading to discontinuation	0	0			0	1 (1.0)	0
Leading to interruption	1 (0.3)	0			0	1 (1.0)	0
Mild	37 (10.0)	61 (16.5)			8 (7.9)	9 (8.7)	2 (3.4)
Moderate	12 (3.2)	20 (5.4)			1 (1.0)	2 (1.9)	0
Severe	2 (0.5)	0			0	0	0
Life-threatening	0	0			0	0	0
Reactive Airways							
Any AE of reactive airways	20 (5.4)	24 (6.5)	Not reported as an AESI				
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					
Respiratory Events							
Any AE of respiratory events	Not reported as an AESI		12 (33.3)	6 (17.6)	13 (12.9)	19 (18.4)	4 (6.9)
Chest discomfort			0	0	1 (1.0)	0	0
Dyspnea			3 (8.3)	1 (2.9)	5 (5.0)	5 (4.9)	1 (1.7)
Abnormal respiration			19 (25.0)	5 (14.7)	4 (4.0)	6 (5.8)	1 (1.7)
Asthma			0	0	1 (1.0)	4 (3.9)	0
Wheezing			1 (2.8)	0	3 (3.0)	5 (4.9)	2 (3.4)
Leading to discontinuation			Not reported		0	1 (1.0)	0
Leading to interruption					0	1 (1.0)	0
Mild					10 (9.9)	15 (14.6)	4 (6.9)
Moderate					3 (3.0)	4 (3.9)	0
Severe					0	0	0
Life-threatening					0	0	0

AE = adverse event; AESI = adverse event of special interest; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours.

Source: Common Technical Document[4] and clinical study reports.[1,2,6-8]

Table 30: Timing of Onset and Duration of Respiratory Adverse Events

Adverse Events, n (%)	≥ 12 years		6 Years to 11 Years		
	TRAFFIC and TRANSPORT		Study 109		Study 11B
	Placebo (N = 370)	L400/IVA (N = 369)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Respiratory Symptoms					
Any events, n (%)	51 (13.8)	81 (22.0)	9 (8.9)	11 (10.7)	2 (3.4)
> 0 to ≤ 1 week	14 (3.8)	65 (17.6)	4 (4.0)	7 (6.8)	1 (1.7)
> 1 to ≤ 2 weeks	4 (1.1)	4 (1.1)	1 (1.0)	2 (1.9)	0
> 2 to ≤ 8 weeks	17 (4.6)	10 (2.7)	1 (1.0)	2 (1.9)	1 (1.7)
> 8 to ≤ 16 weeks	14 (3.8)	8 (2.2)	2 (2.0)	1 (1.0)	1 (1.7)
> 16 to ≤ 24 weeks	9 (2.4)	8 (2.2)	3 (3.0)	1 (1.0)	0
> 24 weeks	1 (0.3)	1 (0.3)	0	0	0
Time to onset (days)					
Mean (SD)	51.7 (51.53)	18.9 (41.52)	51.4 (66.11)	44.5 (51.22)	50.5 (70.00)
Median (range)	43.0	2.0	10.0 (1, 153)	17.0 (1, 144)	50.5 (1, 100)
Duration of events (days)					
Number of events	65	102	11	13	2
Mean (SD)	12.9 (15.01)	18.5 (26.52)	7.3 (8.69)	12.7 (21.20)	1.0 (0.00)
Median (range)	6.5	6.0	3.0 (1, 22)	3.0 (1, 64)	1.0 (1, 1)
Reactive Airways					
Any events, n (%)	20 (5.4)	24 (6.5)	Not reported as an AESI		
> 0 to ≤ 1 week	6 (1.6)	8 (2.2)			
> 1 to ≤ 2 weeks	2 (0.5)	3 (0.8)			
> 2 to ≤ 8 weeks	8 (2.2)	6 (1.6)			
> 8 to ≤ 16 weeks	4 (1.1)	8 (2.2)			
> 16 to ≤ 24 weeks	2 (0.5)	3 (0.8)			
> 24 weeks	0	0			
Time to onset (days)					
Mean (SD)	34.3 (33.28)	48.3 (46.77)			
Median (range)	22.0	50.0			
Duration of events (days)					
Number of events	23	30			
Mean (SD)	14.6 (15.00)	20.6 (39.97)			
Median (range)	10.0	6.0			
Respiratory Events					
Any events, n (%)	Not Reported as an AESI		13 (12.9)	19 (18.4)	4 (6.9)
> 0 to ≤ 1 week			6 (5.9)	8 (7.8)	1 (1.7)
> 1 to ≤ 2 weeks			1 (1.0)	2 (1.9)	0
> 2 to ≤ 8 weeks			1 (1.0)	3 (2.9)	2 (3.4)
> 8 to ≤ 16 weeks			2 (2.0)	7 (6.8)	1 (1.7)
> 16 to ≤ 24 weeks			5 (5.0)	2 (1.9)	0
> 24 weeks			0	0	0
Time to onset (days)					
Mean (SD)			57.2 (68.24)	44.5 (51.22)	46.3 (42.07)
Median (range)			10.0 (1, 159)	17.0 (1, 144)	42.0 (1, 100)
Duration of events (days)					

Adverse Events, n (%)	≥ 12 years		6 Years to 11 Years		
	TRAFFIC and TRANSPORT		Study 109		Study 11B
	Placebo (N = 370)	L400/IVA (N = 369)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Number of events			15	22	4
Mean (SD)			9.4 (12.82)	20.7 (38.96)	1.3 (0.58)
Median (range)			3.0 (1, 45)	8.5 (1, 169)	1.0 (1, 2)

AESI = adverse event of special interest; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; SD = standard deviation.

Source: Common Technical Document[4] and clinical study reports.[1,2,6-8]

Ophthalmic Adverse Events

AEs classified as eye disorders are summarized in Table 31. One patient in each group in Study 109 and one patient in Study 11B were reported to have experienced a cataract as an AE during the study.[6,7]

Table 31: Timing of Onset and Duration of Respiratory Adverse Events

Eye Disorders, N (%)	≥ 12 years				6 Years to 11 Years		
	TRAFFIC		TRANSPORT		Study 109		Study 11B
	Placebo (N = 184)	L400/IVA (N = 182)	Placebo (N = 187)	L400/IVA (N = 187)	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA (N = 58)
Eye disorders	3 (1.6)	5 (2.7)	5 (2.7)	6 (3.2)	6 (5.9)	10 (9.7)	3 (5.2)
Asthenopia	1 (0.5)	1 (0.5)	0	0	0	0	0
Astigmatism	0	0	0	0	0	0	0
Blepharospasm	0	1 (0.5)	0	2 (1.1)	0	1 (1.0)	0
Blindness transient	0	0	1 (0.5)	0	0	0	0
Cataract	0	0	0	0	1 (1.0)	1 (1.0)	1 (1.7)
Chalazion	0	0	0	0	1 (1.0)	0	0
Conjunctival disorder	0	0	0	0	1 (1.0)	0	0
Conjunctivitis allergic	1 (0.5)	0	0	0	1 (1.0)	0	0
Erythema of eyelid	0	0	0	0	1 (1.0)	0	0
Eye irritation	0	0	1 (0.5)	0	1 (1.0)	0	0
Eye pain	0	0	1 (0.5)	0	0	0	0
Eye pruritus	0	0	1 (0.5)	0	0	0	2 (3.4)
Eye swelling	0	0	0	1 (0.5)	0	0	0
Eyelid oedema	0	0	0	0	1 (1.0)	0	0
Lacrimation increased	0	0	0	0	0	2 (1.9)	0
Myopia	0	0	0	0	0	2 (1.9)	0
Ocular hyperaemia	0	0	0	0	0	0	0
Periorbital oedema	1 (0.5)	0	0	0	0	0	0
Photopsia	0	0	0	1 (0.5)	0	0	0
Vision blurred	1 (0.5)	2 (1.1)	0	2 (1.1)	1 (1.0)	1 (1.0)	0
Visual acuity reduced	0	1 (0.5)	0	1 (0.5)	1 (1.0)	3 (2.9)	0

L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours.

Source: Clinical study reports.[1,2,6-8]

Discussion

Summary of Available Evidence

CADTH previously reviewed L400/IVA for treatment of CF in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. Following the completion of CADTH's review, the Health Canada–approved indication was subsequently expanded to include patients who are at least six years of age. The current CADTH review is for the full Health Canada–approved indication (i.e., evidence for the originally reviewed population and new expanded population has been included). The evidence for this updated review was derived from the following studies: four DB placebo-controlled RCTs (TRAFFIC, TRANSPORT, Study 112, and Study 109); a pivotal, single-arm, open-label study (Study 11B); two extension phase studies (PROGRESS and Study 110); and a single-arm study conducted in patients with severe lung disease (Study 106). The study populations consisted of patients who were either six years to 11 years of age (studies 109, 11B, and 110) or patients who were at least 12 years of age (TRAFFIC, TRANSPORT, PROGRESS, and studies 106 and 112).

TRAFFIC and TRANSPORT were the pivotal studies for patients 12 years and older and were reviewed as part of the previous CADTH review of L400/IVA. These were identically designed phase III, randomized, DB, placebo-controlled studies conducted to evaluate the efficacy and safety of LUM/IVA in patients with CF homozygous for the F508del-CFTR mutation aged 12 years and older (TRAFFIC and TRANSPORT). The CADTH 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 daily/IVA 250 mg every 12 hours), which was excluded from the CADTH review as it is not currently recommended in the product monograph and could not be achieved using the formulations of LUM/IVA that are marketed in Canada (i.e., tablets containing 100 mg or 200 mg of LUM and 125 mg of ivacaftor). Study 112 (N = 70) was also conducted in patients aged 12 years and older. This recently completed study was a small phase 4, placebo-controlled RCT conducted to evaluate the effect of L400/IVA on manifestations of CF affected by exercise tolerance and training.

The included studies for patients aged six years to 11 years consisted of a pivotal, open-label, single-arm trial (Study 11B) and a DB, placebo-controlled RCT (Study 109). As reflected in the Canadian product monograph, these studies used a lower dosage of LUM (200 mg of every 12 hours) than is currently used in patients older than 12 years of age. Health Canada considered Study 11B to be pivotal for safety, but not for efficacy due to the lack of a control group. The Canadian efficacy assessment for patient six years to 11 years of age was based on extrapolation of the data from the TRAFFIC and TRANSPORT studies (i.e., patients 12 years of age and older).[67] In contrast, the review by EMA also considered the results of Study 109.

The DB RCTs included in this review were generally well-conducted. TRAFFIC, TRANSPORT, and Study 109 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 (e.g., EQ-5D-3L), symptoms (CFQ-R respiratory domain), and clinical events (e.g., pulmonary exacerbations). The manufacturer reported that the TRAFFIC and TRANSPORT trials did not include changes in sweat chloride, a commonly used biochemical marker in

CF trials, as the effect of L400/IVA on sweat chloride was established in the phase II studies of the clinical development program.[34] Conversely, changes in sweat chloride were included as secondary end points in studies 109 and 11B.[6,7]

All of the studies, with the exception of Study 109, excluded patients who were infected with some *Burkholderia cepacia* complex species (i.e., *Burkholderia cenocepacia* and *Burkholderia dolosa*). These patients represent 3.8% of the overall CF patient population in Canada;[13] however, the clinical experts consulted by CADTH 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, where it was suggested that there is no basis to conclude that patients with CF with these infections would not benefit from treatment with LUM/IVA.[64] 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.[64] In the initial CADTH review, the manufacturer stated that it was conducting post-market studies to collect data on the use of LUM/IVA in patients infected with *Burkholderia cepacia* complex species (details were not provided); however, until these data are available, this remains a relevant research gap for the adult CF patient population. In Study 109, only three patients (1.5%) were positive for cultures of *Burkholderia cepacia* complex species; however, these bacterial infections are more common in adults (142 out of 160 [88.8%] of all cases in Canada were reported in adults).[13]

Interpretation of Results

Efficacy

Patients 12 Years and Older

Potential improvements in lung function can be evaluated based on short-term changes from baseline (e.g., absolute or relative change from baseline in $ppFEV_1$ or $LCI_{2.5}$) or long-term changes evaluating the impact of an intervention on the course of CF The data included in this review of LUM/IVA includes data for short-term changes, as evaluated in the clinical trials for LUM/IVA; and longer-term changes, as assessed and modelled in PROGRESS and the matched cohort study. When considering lung function measurements in a chronic condition such as CF, the clinical experts consulted by CADTH indicated that the ability of a treatment such as LUM/IVA to result in long-term changes is generally considered to be more clinically relevant than acute changes in $ppFEV_1$. Similar statements have been made by regulatory authorities (Health Canada and EMA)[11,25] and health technology assessment agencies (NICE and the Australian Pharmaceutical Benefits Advisory Committee [PBAC]).[70,71] As both short-term and long-term analyses of $ppFEV_1$ were submitted by the manufacturer, the potential clinical relevance of each type of analysis is subsequently discussed.

With respect to the data from the short-term studies (i.e., 24 weeks), L400/IVA was associated with a statistically significant improvement in $ppFEV_1$ compared with placebo (absolute improvement of 2.6% to 3.0%). Placebo-treated patients who were crossed over to L400/IVA in the PROGRESS study also demonstrated an increase from baseline in $ppFEV_1$ at 24 weeks (3.4%). 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.[25] The clinical experts consulted for this review indicated that a short-term change in $ppFEV_1$ of the magnitude observed in the TRAFFIC and

TRANSPORT studies was modest and of uncertain clinical benefit. While no published information on the MCID in absolute change in $ppFEV_1$ in CF was identified by CADTH, the clinical experts consulted by CADTH noted that CF specialists would generally consider an absolute improvement in $ppFEV_1$ of at least 5% to be clinically relevant. This was also the threshold cited by the clinical expert consulted by the NICE Evidence Review Group in the UK.[70]

In a responder analysis, 26.8% of L400/IVA-treated patients in TRAFFIC and TRANSPORT achieved an absolute increase of at least 5% in $ppFEV_1$ compared with 14.0% in the placebo group (odds ratio: 2.26 [95% CI, 1.55 to 3.29]). 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 criteria that could be used to identify nonresponders shortly after the initiation or treatment; and, stopping criteria to avoid unnecessary exposure of patients who are unlikely to benefit clinically from treatment with L400/IVA.[25] However, since L400/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 nonresponders should not be based on early $ppFEV_1$ response.[25]

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 IVA monotherapy in the treatment of patients with CF with gating mutations (STRIVE, ENVISION, and KONNECTION).[59-61] It is also lower than the 5.0% improvement in $ppFEV_1$ that was observed with IVA in adults with the R117H mutation (KONDUCT).[62] 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.[25]

Although the magnitude of improvement in the short-term analyses is modest, 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.[25,72,73] Given the correlation between lung function and mortality in CF, Health Canada concluded that any of the following could be considered clinically relevant for patients with CF: stabilization of lung function, an improvement in the rate of decline of lung function, or a marginal improvement in lung function.[73] Similarly, the draft recommendation from the NICE technology appraisal committee that was cited in the initial CADTH review stated that the improvements in $ppFEV_1$ that were observed with L400/IVA in the pivotal studies were unlikely to be clinically significant; however, the conclusion in the final recommendation was that long-term changes in $ppFEV_1$ were more clinically relevant than acute changes for assessing long-term outcomes of CF.[70]

The ability of an intervention to result in long-term changes in lung function is a more accurate reflection of CF treatment goals and is considered to be a more clinically relevant end point than acute changes in $ppFEV_1$.[11,25,70,71] However, TRAFFIC and TRANSPORT were too short to draw conclusions regarding whether or not treatment with L400/IVA would reduce the slope of decline in $ppFEV_1$. The initial CADTH review of L400/IVA considered the 24-week data from the first interim analysis of the PROGRESS extension study, which suggested that patients treated with L400/IVA maintained the effects that were observed in the DB phase of TRAFFIC and TRANSPORT (absolute improvement of 2.5% from

baseline; $P < 0.0001$). Since the initial CADTH review, the manufacturer has provided additional long-term follow-up data for L400/IVA (i.e., for the final 96-week data from PROGRESS). For patients who were treated with L400/IVA in TRAFFIC and TRANSPORT, the absolute improvement in $ppFEV_1$ was gradually reduced throughout the PROGRESS study, from 2.7% (95% CI, 1.8 to 3.6) at 24 weeks, to 1.4% (95% CI, 0.5 to 2.4) at 48 weeks, and 0.5% (95% CI, –0.4 to 1.5) in the primary analysis at 72 weeks. Results were similar in those who were treated with placebo in TRAFFIC and TRANSPORT and crossed over to L400/IVA in PROGRESS (i.e., initial improvement of 3.4% [95% CI, 2.2 to 4.7] at 24 weeks, 2.1% [95% CI, 0.8 to 3.4] at 48 weeks, and 1.5% [95% CI, 0.2 to 2.9] at 72 weeks).

With respect to evaluating the impact of LUM/IVA on the rate of lung function decline in patients with CF, the manufacturer has conducted a post hoc matched-registry cohort analysis (Appendix 6). This matched-registry cohort analysis compared patients with CF treated with L400/IVA from PROGRESS (N = 455) with patients from the US Cystic Fibrosis Foundation Patient Registry (N = 1,588). The analysis suggested that the slope of decline in lung function (i.e., $ppFEV_1$) was reduced in patients who were treated with L400/IVA compared with a matched cohort of patients from the US registry (–1.33% versus –2.29% per year over a two-year period). CADTH identified a number of important limitations with the cohort analysis that limit the ability to draw conclusions regarding the impact of L400/IVA on the long-term lung function of Canadian patients with CF. The following key issues with the study may have biased the results in favour of L400/IVA: use of registry patients exclusively from the US as it has been documented that outcomes for US patients with CF are worse than Canadian patients with CF;[74] the generation of propensity scores did not include some important potential confounders (e.g., pulmonary exacerbation frequency and socioeconomic status); the balance across the full range of patients and important subgroups were not presented, thus whether balance was fully achieved and how this may have affected the study results is uncertain.

The limitations with the matched cohort analysis were also documented by PBAC, which noted that the analysis did not adequately support the manufacturer's claim that treatment with L400/IVA reduced the rate of decline in FEV_1 compared with best supportive care and that the comparison was likely biased in favour of L400/IVA.[75] PBAC cited concerns with comparability between the cohort and trial populations (e.g., multinational trial population receiving extensive contact with health professionals in a specialized setting versus a cohort of patients from the US) and the generalizability of the study given that patients with CF in the US have had a poorer prognosis than other jurisdictions (e.g., Canada and the UK).[75] The clinical experts consulted by CADTH also expressed concern regarding the comparability of Canadian patients with those on the US registry and the potential for residual confounding in the registry comparator analysis. Overall, due to the limitations regarding the long-term extension data and the matched cohort comparison (i.e., absence of a control group, high rate of discontinuation, and generalizability concerns), there remains uncertainty regarding the long-term impact of treatment with LUM/IVA on the lung function of patients with CF. The Institute for Clinical and Economic Review in the US reached a similar conclusion, noting that there is evidence that CFTR modulators improve lung function over the short-term, but that data on their ability to slow the longer-term rate of decline in lung function is still developing.[76]

Pulmonary exacerbations are currently the most common reason for hospitalization of patients with CF[12] and, accordingly, these events were identified as an outcome of interest by Cystic Fibrosis Canada in its input on 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.[77-81] In addition, it has been estimated that many patients with CF 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 patients with CF (N = 8,479), Sanders et al. (2010) estimated that 25% of patients with CF who experienced a pulmonary exacerbation failed to recover to their baseline FEV_1.[82] A similar observation has been made in an analysis in pediatric patients with CF where 23% of patients failed to recover to their baseline FEV_1 after being treated with IV antibiotics for a pulmonary exacerbation.[83]

Treatment with L400/IVA was associated with a 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 L400/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 experts consulted by CADTH, that the observed reduction in pulmonary exacerbations with L400/IVA is likely to be clinically meaningful; however, claims of statistical significance cannot be made.[25,40] Throughout the PROGRESS study, the improvement in the rate of pulmonary exacerbations that was observed in the TRAFFIC and TRANSPORT studies appeared to be maintained. In addition, placebo-treated patients who received L400/IVA experienced a lower rate of pulmonary exacerbations compared with the rate during the TRAFFIC and TRANSPORT studies (0.69 versus 1.19 events per patient, per year, at 96 weeks of follow-up).

The treatment effect with L400/IVA was relatively consistent across all of the subgroups that were studied in TRAFFIC and TRANSPORT; however, due to the small number of patients, interpretation of the results for some subgroup analyses (e.g., $ppFEV_1 < 40\%$ or ages 12 years to 18 years) is limited by wide CIs with the estimates of effect. 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%.[25] 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 patients with CF. 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 L400/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 L400/IVA (e.g., BMI z scores of −0.36 at baseline, −0.20 at 24 weeks, and −0.13 at 48 weeks). Similar to those who were treated with L400/IVA in the TRAFFIC and TRANSPORT studies, placebo-treated patients who were crossed over to L400/IVA in the PROGRESS study demonstrated an increase from

baseline in BMI at 24 weeks (LSM change of 0.41 kg/m^2 [95% CI, 0.24 to 0.57]). The BMI of L400/IVA-treated patients continued to increase throughout the PROGRESS study, with an LSM change from baseline of 0.69 kg/m^2 and 0.62 kg/m^2 at week 72 for the L400/IVA and placebo-to-L400/IVA groups, respectively. Given the relative short-term data available, the clinical relevance of the observed changes in BMI is uncertain; however, reviewers for the FDA commented that L400/IVA failed to demonstrate consistent clinical benefit in BMI.[54]

As stated in the patient group input, CF has a major impact on the quality of life of patients and their caregivers. Treatment with L400/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. Given that mean baseline score was close to 1.0 (i.e., perfect health as defined by the instrument) there would be little room for patients to improve their EQ-5D utility score in both the TRAFFIC and TRANSPORT trials. However, the EQ-5D has not been formally evaluated as a measure of health-related quality of life in CF.[40] This perspective was shared by patient experts who provided input on NICE's review of L400/IVA.[40] It must be noted that the use of IVA monotherapy in patients with CF-gating mutations was associated with greater improvements in the CFQ-R (i.e., 6.1% to 8.1%)[59,60] than was observed with L400/IVA in TRAFFIC and TRANSPORT. In addition, treatment with IVA resulted in a statistically significant improvement in EQ-5D compared with placebo, though the magnitude of improvement was not considered to be clinically relevant.

Study 112 was a small study that was not designed or powered to detect differences in the end points of interest for CADTH's review. There was no difference between L400/IVA and placebo in Study 112 for absolute change from baseline in ppFEV$_1$, relative change from baseline in ppFEV$_1$, absolute change from baseline in BMI, or absolute change from baseline in CFQ-R respiratory domain. Study 112 was designed to evaluate the effect of L400/IVA on manifestations of CF affected by exercise tolerance and training.[37] The primary end point and key secondary end point were not met, as treatment with L400/IVA did not demonstrate a statistically significant difference in VO2$_{max}$ or exercise duration during cardiopulmonary exercise testing relative to placebo at 24 weeks (1.3 mL/kg/min [95% CI, –3.8 to 6.5] and –6.8 s [95% CI, –40.4 to 26.9]).

L400/IVA was studied as an add-on treatment to a stable regimen of CF therapy. There is no evidence to suggest that L400/IVA may replace or minimize the need for current treatments that are used on a daily basis. However, treatment with L400/IVA was associated with a reduction in the need for IV antibiotics and hospitalization — important outcomes that could reduce the overall treatment burden for patients with CF and their caregivers.[25]

Cystic Fibrosis Canada provided patient group input on this review and has also published recommendations from a physician panel regarding the use of L400/IVA in patients aged 12 years and older. The panel recommended that the response to L400/IVA should be determined by demonstrating any one of the following criteria:[84]

- evaluation of ppFEV$_1$:
  - relative change of at least 5%
  - absolute change of at least 5%
  - maintenance of lung function during treatment
- reduction in pulmonary exacerbations

- reduction in hospitalizations, or courses of IV antibiotics, related to pulmonary exacerbations
- improvement in weight, or weight percentiles (if less than 18 years) by at least 5%

improvement in BMI or BMI percentiles (if less than 18 years) by at least 5%.

The clinical practice guidelines from the US Cystic Fibrosis Foundation recommend the use of L400/IVA for patients 12 years and older (strong recommendations for those with $ppFEV_1$ < 40% and between 40% and 90%; conditional recommendations for those with $ppFEV_1$ above 90%).[85]

Patients Aged Six Years to 11 Years

L200/IVA was associated with a statistically significant improvement in $LCI_{2.5}$ compared with placebo after 24 weeks of treatment (absolute reduction of –1.09). LCI is not currently used in Canadian clinical practice to evaluate lung function in patients with CF, but has been recommended for use as an end point in clinical trials conducted in younger patients. This is because spirometry may not be sensitive enough to detect treatment differences in patients who have relatively normal lung function, but may still have underlying structural abnormalities in the lungs. Due the absence of validation as a surrogate end point, Health Canada asked the manufacturer to provide additional information to support the clinical relevance of the improvement in LCI that was reported with L200/IVA treatment. In response, the manufacturer indicated that LCI is correlated with FEV_1 in its ability to measure airway disease, which has been validated as an end point.[67] Health Canada reviewers noted that the manufacturer cited a workshop hosted by the EMA on end points in CF clinical trials as the source for the –1 improvement being clinically relevant, though that particular report indicates that the MCID for this end point has not been established. In the Institute for Quality and Efficiency in Health Care's evaluation of L200/IVA, $LCI_{2.5}$ was not considered in its benefit assessment as it was not considered to be a validated surrogate end point in patients with CF.[86] The clinical experts consulted by CADTH indicated that it is uncertain what magnitude of improvement in $LCI_{2.5}$ would be considered clinical relevant.

Similar to the TRAFFIC and TRANSPORT studies, treatment with L200/IVA resulted in an improvement in $ppFEV_1$ after 24 weeks of treatment compared with placebo in Study 109 (LSMD: 2.4% [95% CI, 0.4 to 4.4]). It should also be noted that analyses for change from baseline in $ppFEV_1$ in Study 109 were not adjusted for multiplicity and should interpreted accordingly. Although the magnitude of the improvement relative to placebo was similar in Study 109 (2.4%) and TRAFFIC and TRANSPORT (2.6% to 3.0%), the mean changes observed within the treatment and placebo groups differed across the studies. Specifically, the mean increase in $ppFEV_1$ in the pooled L400/IVA treatment groups was 2.5% and the mean decrease in the pooled placebo groups was –0.3% in TRAFFIC and TRANSPORT. In Study 109, the increase in $ppFEV_1$ with L200/IVA was 1.1% and the decrease in the placebo group was –1.3%.[7] Data from the Canadian Cystic Fibrosis Registry (2013) suggested that patients with CF undergo a decline in lung function of 0.2% per year between the ages of 6 years and 11 years; hence, the decrease of –1.3% at 24 weeks reported for the placebo group of Study 109 may not be reflective of Canadian patients.[69] The clinical expert consulted by CADTH suggested that this would not be reflective of the decline expected in Canadian patients and could be due to challenges performing the FEV_1 measurement in a younger patient population. The limitations of spirometry testing in younger children with relative normal lung function have been documented by regulatory

authorities[48] and were an important consideration in the manufacturer's decision to use $LCI_{2.5}$ as the primary end point of Study 109.[7] In Study 11B, treatment with L200/IVA was not associated with a statistically significant improvement in $ppFEV_1$ after 24 weeks (2.5% [95% CI, –0.2 to 5.2]); however, reviewers for the EMA stated that the results suggested the potential for improvement in respiratory function (due to the limitations of the spirometry test and in conjunction with the improvements observed in $LCI_{2.5}$).[57]

There was no statistically significant difference between the L200/IVA group and the placebo group of Study 109 for the nutritional end points (i.e., BMI, BMI-for-age z score, weight, weight-for-age z score, height, or height-for-age z score). Reviewers for the EMA noted that there appeared to be a trend toward improvement in BMI with L200/IVA in Study 109 (0.11 [95% CI, −0.08 to 0.31]), but noted that there is insufficient evidence to confirm that the potential improvement in BMI was due to improved pancreatic function from L200/IVA. Study 11B demonstrated within-group improvements from baseline in all nutritional end points with the exception of height-for-age z score; however, it should be noted that the comparisons were not adjusted for multiplicity and should be interpreted accordingly. It is also challenging to interpret these results in the absence of a control group given that the trial involved extensive contact with health professionals. In addition, it is unclear why the improvements in BMI z scores were greater with L200/IVA treatment in Study 11B (i.e., increase of 0.15 [0.04]) compared with Study 109 (i.e., increase of 0.08 [0.04]). A clinical expert consulted by CADTH suggested that 24 weeks is unlikely to be enough time to observe meaningful changes in BMI, particularly in a younger CF patient population that is relatively healthy. CF Canada has reported that one of the treatment goals for children with CF is to obtain a BMI within the 50th percentile (noting that 45.6% of Canadian patients with CF aged 2 years to 17 years have achieved this goal). The EMA reported the results of a post hoc responder analysis stating that among patients with a BMI-for-age z score of less than zero in Study 109, a greater proportion of L200/IVA-treated patients had a BMI value within the 50th percentile after 24 weeks compared with the placebo group (14.8% versus 7.7%). The EMA noted that this result suggested that L200/IVA had a positive effect on BMI in young patients with CF who were undernourished.[57] A clinical expert consulted by CADTH also noted that achieving the goal of 50th percentile is clinically important for patients who are failing to thrive, but that such pediatric patients would likely receive additional clinical assistance in Canada (e.g., review of dietary supplements) to try and achieve this treatment goal.

There was no statistically significant difference between the L200/IVA and placebo group in the rate of pulmonary exacerbations in Study 109 (rate ratio: 1.33 [95% CI, 0.70 to 2.53]). Pulmonary exacerbations were less frequent in the studies that enrolled patients six years to 11 years of age (19.4% versus 14.9% with L200/IVA and placebo, respectively) compared with the TRAFFIC and TRANSPORT studies (39.7% to 47.1% versus 28.9% to 30.2% with L400/IVA and placebo, respectively). The clinical experts consulted by CADTH indicated that this is reflective of clinical practice, where these events are less common in children with relatively normal lung function. It was also noted that a single definition of pulmonary exacerbation for use in both pediatric and older patients may not be the best approach, as the reporting and management of exacerbations in pediatric patients can be different from adults and adolescents (e.g., differences in the reporting of symptoms by parents and caregivers).

There was no statistically significant difference in CFQ-R respiratory domain scores after 24 weeks. Reviewers for the EMA noted that the failure to demonstrate improvement in the

CFQ-R was not a major concern as the instrument may not be able to detect treatment differences in young patients who are at an early stage of disease.[57]

Cystic Fibrosis Canada has not published recommended clinical criteria or guidelines regarding the use of LUM/IVA in patients aged six years to 11 years of age. The clinical practice guidelines from the US Cystic Fibrosis Foundation recommend the use of L200/IVA for these patients (conditional recommendations for all $ppFEV_1$ subgroups [i.e., < 40%, 40% to 90%, > 90%]).[85]

Harms

Both L400/IVA and L200/IVA appear to be generally well-tolerated in the target patient populations (i.e., at least 12 years of age and between six years and 11 years of age, respectively). The most common AEs associated with LUM/IVA were respiratory and gastrointestinal. WDAEs were more common in the L400/IVA group than in the placebo group in both pivotal studies; however, over 95% of LUM/IVA-treated patients completed the 24-week treatment period. The clinical expert consulted by CADTH noted that patients who experience significant AEs following initial treatment with LUM/IVA would not likely be completely discontinued from treatment; rather, treatment with LUM/IVA would likely 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 AEs in patients receiving LUM/IVA and it is recommend that patients be monitored, particularly during the phase when treatment is being initiated.[24] The clinical expert consulted by CADTH 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.[65]

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 CADTH 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 IVA development program,[59,60,62] patients with abnormal liver function were excluded from TRAFFIC, TRANSPORT, and studies 11B, 109, and 112.[1,2,6-8]

L400/IVA was associated with an increase in the occurrence of respiratory AEs (e.g., dyspnea and abnormal respiration) compared with placebo in TRAFFIC and TRANSPORT (though the opposite was observed in Study 112, with these events being more commonly reported in the placebo group). Nearly all of the events were mild to moderate in severity, occurred shortly after the initiation of treatment, and were typically resolved within a few weeks of treatment. The respiratory AEs occurred more frequently in patients with poorer lung function in TRAFFIC and TRANSPORT; however, the severity of these events was generally similar regardless of baseline lung function.[87] Study 106 was conducted in patients with $ppFEV_1$ less than 40% and a majority (65%) of LUM/IVA-treated patients reported respiratory AEs, with 13% discontinuing treatment as a result of these events.[28,29] The Canadian product monograph currently contains a warning regarding the observed increase in respiratory AEs with LUM/IVA, which 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.[24] A clinical expert consulted by CADTH noted that the issue of respiratory AEs 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.

With the L200/IVA dosage in the younger patient population of Study 109, the proportion of patients with respiratory symptom AEs was similar between the L200/IVA and placebo groups (10.7% versus 8.9%, respectively) and the overall frequency of respiratory AEs was greater in the L200/IVA group compared with the placebo group (18.4% versus 12.9%). Similar to the TRAFFIC and TRANSPORT studies, these events were generally mild or moderate in severity, with one L200/IVA-treated patient discontinuing treatment as a result of these events.[7]

In Study 109, there were several AEs that occurred more frequently in L200/IVA-treated patients compared with the placebo group that were not observed in the studies conducted in the older patient populations. These included increases in the proportion of patients with productive cough (17.5% versus 5.9%), nasal congestion (16.5% versus 7.9%), and increased sputum (10.7% versus 2.0%).[7] Given that airway clearance is an important goal of day-to-day management of CF, a clinical expert consulted by CADTH suggested that the increase in productive cough, increased sputum, and nasal congestion could potentially be beneficial for patients and an indication that the treatment is working (i.e., mucus is beginning to clear from airways and sinuses).

Other Considerations

NICE in the UK has issued a recommendation stating that it does not recommend that L400/IVA be funded for treating CF in people 12 years and older who are homozygous for the F508del mutation in the CFTR gene.[70] NICE's decision appeared to be predominately based on the fact that the L400/IVA would not be considered a cost-effective use of resources. Similarly, the Scottish Medicines Consortium (SMC) also concluded that L400/IVA was not recommended for use within NHS Scotland. The SMC noted that the cost of L400/IVA relative to the health benefits it offered was insufficient.[88] PBAC in Australia had issued several decisions stating that L400/IVA was not recommended for listing on the Pharmaceutical Benefits Scheme, citing unacceptably high and uncertain incremental cost-effectiveness and uncertainty around the impact of L400/IVA on long-term improvements in lung function and survival for CF patients.[89] However, PBAC recently issued a positive recommendation for both L200/IVA and L400/IVA under a managed access program; requesting that further data be collected to demonstrate that differences in the rate of decline in lung function and pulmonary exacerbations are sustained over a period of at least four years in actual clinical practice.[90]

In Germany, the GB-A concluded that L400/IVA demonstrated additional benefit for patients 12 years and older. The Institute for Quality and Efficiency in Health Care in Germany had recommended that additional benefit has not been proven with L200/IVA; however, the final decision from the G-BA was that L200/IVA is associated with a non-quantifiable additional benefit.[86,91] Reviewers for ICER in the US concluded that treatment with LUM/IVA offers a small net health benefit relative to best supportive care (i.e., incremental benefit). In their comments on the draft CDR clinical review, the manufacturer reported that the clinical benefits of L400/IVA have been recognized in the following regions: NHS England, the US,

Australia, Ireland, Germany, France, Denmark, Luxembourg, Austria, and Italy.[92] LUM/IVA was reimbursed in Sweden for patients six years and older as of July 2018.[93]

LUM/IVA is only indicated for use in the treatment of the patients who are homozygous for the F508del mutation. Health Canada recently approved Symdeko (tezacaftor/ivacaftor) for treating the underlying cause of CF in people 12 years and older who have two copies of the F508del mutation in CFTR gene, or who have one copy of the F508del mutation and one of the following mutations in the CFTR gene: P67L, D110H, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.[94]

Potential Place in Therapy[1]

The clinical experts 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 L400/IVA when given in addition to standard CF therapy in phase III trials conducted in patients 12 years and older (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.[79] 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 in Canada.[21,79,95] Reduction in exacerbations is likely the best surrogate marker available. Pulmonary exacerbations are strongly associated with increased mortality and this has been shown in Canadian CF populations, as well as in other countries. Long-term therapy with other CF drugs such as dornase alpha and inhaled antibiotics have been shown to be associated with significant reduction in lung function decline over time[96] and improvement in survival.[97] In phase III clinical trials of six months duration, dornase alpha conferred a 5.8% relative improvement in FEV_1 and a 35% decline in the number of exacerbations, a similar degree of magnitude to that seen with L400/IVA when used in addition to standard of care. Thus, the magnitude of change in number of exacerbations seen with LUM/IVA in the phase III trials is likely 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 patients with CF have had their genotype assessed.[12] The goal for therapy in CF is to slow disease progression in order to maximize survival and quality of life. In adult patients, the clinical expert consulted for the review suggested that given the relatively modest results of LUM/IVA when compared with IVA in patients with CF and gating mutations, and the high cost of therapy, 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 L400/IVA. This same principle may apply in the use of L200/IVA in the younger age group (i.e., those six years to 11 years of age), the majority of whom may have normal lung function and BMI and a good quality of

[1] This information is based on information provided in draft form by clinical experts consulted by CADTH for the purpose of this review.

life, making detection of clinical benefit more challenging. However, there are no data on longer-term use of L200/IVA in this age group in terms of maintaining this normal lung function and BMI (i.e., extension phase data are limited to an interim analysis), particularly as these patients move toward adolescence, a period during which decline in both parameters is common.[13]

Patients with $ppFEV_1$ of less than 40% have severe lung disease and shortened survival. Current guidelines suggest referral for lung transplant when $ppFEV_1$ reaches 30%. Although lung transplant is no longer experimental therapy, it is costly and 33% of Canadian patients will die within five years of transplant.[98] These patients do not have the luxury of time to wait for better medical therapies. However, the pivotal TRANSPORT and TRAFFIC trials excluded patients with $ppFEV_1$ less 40% from study; therefore, there is currently no high-quality evidence to suggest that patients with $ppFEV_1 < 40\%$ will benefit from LUM/IVA.

Additionally, the clinical experts indicated that parents of children with CF may want their children to be started on therapy, even if they have minimal lung function impairment, given that the goal of therapy is to prevent disease. However, the clinical experts also noted that the data from clinical trials in children ages six years to 11 years who were treated with L200/IVA suggests that the treatment does not prevent pulmonary exacerbations in this age group. Study 109 demonstrated no statistically significant difference between the L200/IVA and placebo groups in the rate of pulmonary exacerbations (rate ratio: 1.33 [95% CI, 0.70 to 2.53]). In fact, there were a higher percentage of patients with exacerbations in the group treated with L200/IVA as compared with placebo. It should be noted, however, that applying a universal definition for pulmonary exacerbations for both children and adults can be problematic as young children with more mild disease will present with different signs and symptoms than adults with more advanced disease. Children are much more likely to experience virally triggered exacerbations and experience more use of oral antibiotic at a lower threshold than that of adults. Therefore, when use of an intervention (e.g., oral antibiotics) is used to define a pulmonary exacerbation, and when the duration of the study includes viral season, interpretation of change in frequency of pulmonary exacerbations can be challenging.[99]

Conclusions

CADTH reviewed the evidence for the full Health Canada–approved indication for LUM/IVA in this CDR submission, including patients 12 years and older and those aged six years to 11 years of age who are homozygous for the F508del mutation in the CFTR gene. The CADTH systematic review included four DB, placebo-controlled RCTs (TRAFFIC, TRANSPORT, Study 112, and Study 109) and one pivotal single-arm, open-label trial (Study 11B). In addition, CADTH reviewed two extension phase studies (PROGRESS and Study 110) and a single-arm study conducted in patients with severe lung disease (Study 106).

The TRAFFIC and TRANSPORT studies enrolled patients who were at least 12 years of age and had mild-to-moderate lung disease at the time of screening. Both studies demonstrated that 24 weeks of treatment with L400/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%). The manufacturer conducted a matched-registry cohort analysis that suggested the slope of decline in lung function was reduced in patients who were treated with L400/IVA in the PROGRESS study compared with a matched cohort of patients from a US registry (–1.33% versus –2.29% per year over a two-year period). Due to limitations in the analysis, concerns regarding the comparability of the patients from the clinical trials and those from the registry, and issues regarding the generalizability of US registry patients with Canadian patients with CF, it is uncertain if treatment with L400/IVA would have a similar impact on the rate of lung function decline in Canadian patients.

Compared with placebo, L400/IVA demonstrated clinically meaningful reductions in the number and severity of pulmonary exacerbations in patients 12 years and older, including those that required hospitalization and treatment with IV antibiotics, but no conclusions about the statistical significance of these outcomes could be made in TRAFFIC and TRANSPORT due to failure of the statistical testing hierarchy at a higher-order end point. There was inconsistency in the results for changes in BMI, with statistical significance being demonstrated in only one of the trials (TRANSPORT); however, a pre-planned pooled analysis suggests that treatment with L400/IVA was associated with improvements in BMI, though the magnitude of improvement was of uncertain clinical significance. Treatment with L400/IVA was not associated with statistically significant or clinically relevant improvements in health-related quality of life at 24 weeks. Treatment with L400/IVA demonstrated similar effects on $ppFEV_1$, BMI, and pulmonary exacerbations in patients who received placebo in TRAFFIC and TRANSPORT and transitioned to L400/IVA in the PROGRESS study.

In patients aged six years to 11 years of age, L200/IVA was associated with a statistically significant improvement in $LCI_{2.5}$ compared with placebo after 24 weeks of treatment (absolute reduction of –1.09). The clinical significance of this finding is uncertain as the MCID has not been established for this end point and it is not currently used in Canadian clinical practice. Treatment with L200/IVA resulted in an improvement in $ppFEV_1$ after 24 weeks of treatment compared with placebo (2.4%); however, the clinical significance of this result is uncertain. Treatment with L200/IVA was not associated with statistically significant improvements in nutritional end points (i.e., BMI, BMI-for-age z score, weight, weight-for-age z score, height, or height-for-age z score), rate of pulmonary exacerbations, or CFQ-R respiratory domain compared with placebo. None of the secondary end points in Study 109 were adjusted for multiplicity.

Both L400/IVA and L200/IVA were generally well-tolerated in the study populations with more than 95% of LUM/IVA-treated patients completing the 24-week treatment periods. In patients aged 12 years and older, L400/IVA was associated with an increased frequency of respiratory AEs (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. Patients aged six years to 11 years treated with L200/IVA experienced fewer respiratory AEs compared with the older patients, possibly due to have better lung function at baseline.

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

Two patient groups, Cystic Fibrosis Canada (CF Canada) and the Cystic Fibrosis Treatment Society (CFTS), responded to CADTH's call for patient input.

CF Canada is a charitable non-profit corporation committed to helping people with cystic fibrosis (CF) to live healthy and well. CF Canada funds research toward finding a cure and improving clinical care. It also works to improve the services and supports for people with CF. Over the past two years, CF Canada received financial contributions from 19 pharmaceutical companies and Innovative Medicines Canada. This included support in excess of $50,000 from both Vertex Pharmaceuticals and Vertex Pharmaceuticals (Canada), the manufacturer of lumacaftor/ivacaftor. CF Canada stated that the contributions from pharmaceutical companies accounted for 2% to 6% of the organization's overall revenue, year over year. CF Canada developed its submission independently using internal resources to collect and analyze the data presented.

CFTS is a Canadian not for profit organization whose purpose is to advocate for individual patients with CF who require CF drugs or medical therapies. The organization received no funding from pharmaceutical companies and had no help from outside their group to collect and analyze data, or to complete the submission.

2. Condition-Related Information

Information was gathered through a national survey conducted in January and February 2018, testimonials from patients with CF and their families; CF Canada publications, including the 2016 Canadian CF Registry Annual Data Report; plus data from SickKids hospital and Genome Canada. Of the 408 individuals who responded to the survey, data were included from adults living with CF (25%) and parents and caregivers of patients with CF (53%). Information from 22% of the respondents who identified as "other" (i.e., neither a patient nor a caregiver) was excluded from the submission. Data were also gathered through online forums such as Facebook, and direct communication with patients with CF and caregivers of patients with CF.

There are currently more than 4,200 people with CF in Canada. The disease affects all exocrine glands of the body and results in the production of thick, sticky mucus, among other clinical symptoms. The most significant clinical impact is in the lungs, where patients have difficulty in clearing secretions, which in combination with aberrant inflammation leads to persistent infections. This may cause progressive scarring of the airways and a progressive and sometimes rapid decline in lung function, leading to respiratory failure, which is the main cause of death in patients with CF. CF also affects the digestive system and makes maintaining body weight a challenge. Although there has been significant progress in treatment and care, of the 46 Canadian patients who died in 2016 of CF-related complications, half were under 38.9 years of age (the median age at death in 2016). The most recent data for 2016 shows the estimated median survival age to be 53.3 years of age.

A demanding treatment routine combined with regular visits to specialized CF clinics, acute infections, and episodic exacerbations that frequently lead to hospitalizations all have a significant impact on day-to-day quality of life, and affect life decisions in the areas of education, career, travel, relationships, and family planning. In 2016, there were 2,191

hospitalizations recorded for patients with CF, which added up to almost 29,000 days spent in hospital. Twenty per cent of patients with CF travel more than 250 km to their CF clinic to receive routine care, with the concomitant interruptions on day-to-day life. Caregivers may also have to change their social activities and their employment in order to accommodate the treatment of a loved one with CF.

> *"My 11 year old daughter spends in excess of 26 hours a week trying to stay healthy. The fight against CF is all encompassing for the family. It requires giving up 2 to 7 hours every day for her therapies. The physical therapies take a toll on my and my wife's bodies. We both have repetitive strain injuries and arthritis in our hands, wrists, and shoulder. This commitment requires scheduling all meals and everyone's activities around her therapies. We restrict our social activities to prevent passing on colds and flus…."*

> *"When two of my children were first diagnosed, the doctor told me I'd never go back to work again. It is a full-time job keeping my children healthy. From helping with their physio to clear mucus, frequent CF clinic visits, hospital stays, and on top of that ensuring our third child does not feel left out as a healthy child."*

Due to a serious risk of cross-infection with pathogenic bacteria, people living with CF are isolated from each other; thus, in addition to suffering from increased anxiety and depression, they have limited ability to participate in support groups that are known to help other individuals living with chronic disease. Limited access to the new treatment also creates mental health issues related to the perceived unfair access to what is potentially a life-altering drug.

> *"My 9 year old son has already spent in total over 6 months of his life in the hospital. Each time he is away from school, his friends, his extra-curricular activities, his bed, his family. He is stuck in a hospital room attached to cords and tubes. He's not allowed to leave his room due to infection control. It's complete isolation. Being away from home for 2 weeks at a time affects the whole family. My daughter has developed separation anxiety."*

3. Current Therapy-Related Information

Most patients living with CF take pancreatic enzymes, multi-vitamins, 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 minutes to 60 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. Resistance to antibiotics is a concern, and some may cause kidney damage or staining of the teeth. Corticosteroids used to reduce inflammation have long-term adverse effects and may contribute to the development of CF-related diabetes, which affects 35% of all adults with CF. Persistent infections eventually destroy the lungs and, while lung transplantation may help end-stage patients with CF, 67% of patients with CF survive five years after a lung transplant (median age at transplant was 28.6 years).

4. Expectations About the Drug Being Reviewed

Lumacaftor/ivacaftor is the only disease-modifying therapy available for people with CF who have a homozygous F508del mutation. Unlike the other treatments available, it targets and works to correct the basic defect in CF. Patients' expectations of the new drug include prolonged life with improved quality of life, which allows them to work, study, and participate more fully in social and physical activities. Patients and caregivers also expect fewer hospitalizations, less time missed from school and work, less pain and infections, and less emotional stress. Patients are willing to tolerate adverse effects of the new drug as they believe the potential benefits far outweigh the possible side effects. The treatment burden (two tablets twice a day) is minimal compared with existing therapies for CF.

Patients with experience with lumacaftor/ivacaftor through clinical trials, private insurance, and the manufacturer's compassionate care program report improved lung function (~70%), reduced rate of exacerbations (67% of adults and 74% of children), and improved nutritional status (42% of adults and 85% of children).

> *"I feel better than I ever have in my life. I actually decided to go to post-secondary school to get an education because I now know I'll live long enough and be healthy enough to have a career for the rest of my adult life. My quality of life has increased immensely and my lung function has increased as well. I couldn't be happier!"*

However, some patients endure uncomfortable side effects and not all patients show improvement on lumacaftor/ivacaftor. The most serious side effect appears to be a "tightness" in the chest when starting lumacaftor/ivacaftor, but in general the symptoms fade within weeks or months. CF Canada has also heard from or about patients for whom the side effects were not worth the gain, and who have chosen to stop. There is an expectation that ongoing research will help to develop a genetic test or other predictive tools to determine likely treatment response, as well as to further define starting and stopping criteria.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE ALL 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 20, 2018
Alerts:	Weekly search updates until July 18, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
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
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.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
medall	Ovid database code; MEDLINE ALL 1946 to present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(Orkambi* or "ivacaftor/lumacaftor" or "lumacaftor/ivacaftor").ti,ab,ot,kf,hw,rn,nm.
2	1Y740ILL1Z.rn,nm.
3	(ivacaftor* or kalydeco* or VX770 or VX 770).ti,ab,ot,kf,hw,rn,nm.
4	or/2-3
5	EGP8L81APK.rn,nm.
6	(lumacaftor* or VRT 826809 or VRT826809 or VX809 or VX 809).ti,ab,ot,kf,hw,rn,nm.
7	or/5-6
8	4 and 7
9	1 or 8
10	9 use medall
11	*ivacaftor plus lumacaftor/
12	(Orkambi* or "ivacaftor/lumacaftor" or "lumacaftor/ivacaftor").ti,ab,kw.
13	or/11-12
14	*ivacaftor/
15	(ivacaftor* or kalydeco* or VX770 or VX 770).ti,ab,kw.
16	or/14-15
17	*lumacaftor/
18	(lumacaftor* or vrt 826809 or vrt826809 or vx 809 or vx809).ti,ab,kw.
19	or/17-18
20	16 and 19
21	13 or 20
22	21 use oemezd
23	conference abstract.pt.
24	22 not 23
25	10 or 24
26	remove duplicates from 25

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:	March 2018
Keywords:	Orkambi (lumacaftor/ivacaftor), cystic fibrosis
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: Detailed Outcome Data

Table 32: Change in ppFEV$_1$ at Each Study Visit in TRAFFIC and TRANSPORT

Study	Time	Parameter	Placebo	L400/IVA	L400/IVA vs. Placebo	
					LSMD (95% CI)[a]	*P* value
Absolute Change in ppFEV$_1$						
TRANSPORT	Baseline	n	185	185	–	–
		Mean (SD)	60.37 (14.32)	60.59 (14.01)		
	Day 15	n	176	184	2.45 (1.17 to 3.73)	0.0002
		LSM change (SE)	–0.20 (0.489)	2.25 (0.481)		
	Week 4	n	178	177	2.58 (1.28 to 3.87)	0.0001
		LSM change (SE)	0.25 (0.489)	2.82 (0.488)		
	Week 8	n	175	173	3.35 (1.93 to 4.76)	< 0.0001
		LSM change (SE)	0.01 (0.530)	3.36 (0.530)		
	Week 16	n	181	178	3.35 (1.79 to 4.90)	< 0.0001
		LSM change (SE)	–0.29 (0.580)	3.06 (0.581)		
	Week 24	n	177	173	2.65 (1.06 to 4.24)	0.0011
		LSM change (SE)	–0.02 (0.590)	2.63 (0.593)		
TRAFFIC	Baseline	n	181	180	–	–
		Mean (SD)	60.45 (13.22)	60.48 (14.29)		
	Day 15	n	175	172	2.58 (1.20 to 3.95)	0.0003
		LSM change (SE)	–0.38 (0.512)	2.20 (0.514)		
	Week 4	n	175	172	2.33 (0.84 to 3.82)	0.0022
		LSM change (SE)	0.00 (0.551)	2.33 (0.553)		
	Week 8	n	171	166	3.17 (1.65 to 4.70)	< 0.0001
		LSM change (SE)	–0.22 (0.563)	2.95 (0.567)		
	Week 16	n	172	166	2.78 (1.22 to 4.35)	0.0005
		LSM change (SE)	–0.15 (0.575)	2.63 (0.582)		
	Week 24	n	173	166	2.41 (0.80 to 4.02)	0.0034
		LSM change (SE)	–0.73 (0.590)	1.68 (0.598)		
Relative Change in ppFEV$_1$						
TRANSPORT	Baseline	n	185	185	–	–
		Mean (SD)	60.37 (14.32)	60.59 (14.01)		
	Day 15	n	176	184	4.30 (1.98 to 6.63)	0.0003
		LSM change (SE)	–0.28 (0.888)	4.02 (0.874)		
	Week 4	n	178	177	4.58 (2.23 to 6.93)	0.0001
		LSM change (SE)	0.42 (0.890)	5.00 (0.888)		
	Week 8	n	175	173	5.81 (3.28 to 8.34)	< 0.0001
		LSM change (SE)	0.32 (0.950)	6.13 (0.950)		
	Week 16	n	181	178	5.81 (3.01 to 8.61)	< 0.0001
		LSM change (SE)	–0.15 (1.044)	5.66 (1.046)		
	Week 24	n	177	173	4.69 (1.94 to 7.45)	0.0009
		LSM change (SE)	0.16 (1.027)	4.85 (1.031)		
TRAFFIC	Baseline	n	181	180	–	–
		Mean (SD)	60.45 (13.22)	60.48 (14.29)		
	Day 15	n	175	172	4.61 (2.25 to 6.98)	0.0001
		LSM change (SE)	–0.18 (0.879)	4.43 (0.882)		

Study	Time	Parameter	Placebo	L400/IVA	L400/IVA vs. Placebo	
					LSMD (95% CI)[a]	*P* value
	Week 4	n	175	172	4.20 (1.59 to 6.82)	0.0017
		LSM change (SE)	0.44 (0.965)	4.65 (0.969)		
	Week 8	n	171	166	4.87 (2.20 to 7.54)	0.0004
		LSM change (SE)	0.42 (0.984)	5.30 (0.991)		
	Week 16	n	172	166	4.50 (1.74 to 7.27)	0.0015
		LSM change (SE)	0.17 (1.016)	4.68 (1.027)		
	Week 24	n	173	166	4.15 (1.44 to 6.86)	0.0028
		LSM change (SE)	–0.85 (0.994)	3.30 (1.009)		

CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; SD = standard deviation; SE = standard error; vs. = versus.

[a] Mixed-effects model for repeated measures included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 years versus ≥ 18 years), and $ppFEV_1$ severity at screening (< 70% versus ≥ 70%).[1,2]

Source: Clinical study reports.[1,2]

Table 33: Subgroup Analyses for $ppFEV_1$ in TRAFFIC and TRANSPORT

Study	Subgroup	Parameter	Placebo	L400/IVA	L400/IVA vs. Placebo	
					LSMD (95% CI)[a]	*P* value
Absolute Change from Baseline in $ppFEV_1$						
TRAFFIC	Age (≥ 12 to < 18 years)	n	49	49	4.12 (0.75 to 7.50)	0.0170
		LSM change (SE)	–0.45 (1.217)	3.67 (1.208)		
	Age (≥ 18 years)	n	131	123	2.02 (0.55 to 3.50)	0.0073
		LSM change (SE)	–0.61 (0.541)	1.41 (0.555)		
	$ppFEV_1$ at screening < 70%	n	123	117	2.95 (1.33 to 4.57)	0.0004
		LSM change (SE)	–0.07 (0.611)	2.88 (0.624)		
	$ppFEV_1$ at screening ≥ 70%	n	49	52	2.19 (–0.81 to 5.19)	0.1506
		LSM change (SE)	–0.99 (1.098)	1.20 (1.050)		
	$ppFEV_1$ at baseline < 40%	n	[redacted]	[redacted]	[redacted]	[redacted]
		LSM change (SE)	[redacted]	[redacted]		
	$ppFEV_1$ at baseline ≥ 40%	n	169	161	2.73 (1.26 to 4.20)	0.0003
		LSM change (SE)	–0.44 (0.539)	2.29 (0.546)		
TRANSPORT	Age (≥ 12 to < 18 years)	n	42	44	1.66 (–1.95 to 5.27)	0.3648
		LSM change (SE)	0.77 (1.326)	2.43 (1.282)		
	Age (≥ 18 years)	n	141	136	3.46 (1.92 to 4.99)	<0.0001
		LSM change (SE)	–0.71 (0.560)	2.75 (0.570)		
	$ppFEV_1$ at screening < 70%	n	121	122	3.57 (1.89 to 5.24)	<0.0001
		LSM change (SE)	–0.94 (0.664)	2.63 (0.654)		
	$ppFEV_1$ at screening ≥ 70%	n	57	56	1.62 (–1.26 to 4.50)	0.2693
		LSM change (SE)	1.06 (1.034)	2.68 (1.040)		
	$ppFEV_1$ at baseline < 40%	n	17	17	4.37 (0.91 to 7.82)	0.0145
		LSM change (SE)	–1.43 (1.472)	2.94 (1.588)		
	$ppFEV_1$ at baseline ≥ 40%	n	166	163	2.79 (1.24 to 4.34)	0.0004
		LSM change (SE)	–0.24 (0.574)	2.55 (0.575)		
Relative Change from Baseline in $ppFEV_1$						
TRAFFIC	Age ≥ 12 to < 18 years	n	[redacted]	[redacted]	[redacted]	[redacted]
		LSM change (SE)	[redacted]	[redacted]		

Study	Subgroup	Parameter	Placebo	L400/IVA	L400/IVA vs. Placebo	
					LSMD (95% CI)[a]	*P* value
	Age ≥ 18 years	n	[redacted]	[redacted]	[redacted]	[redacted]
		LSM change (SE)	[redacted]	[redacted]		
	ppFEV$_1$ at screening < 70%	n	[redacted]	[redacted]	[redacted]	[redacted]
		LSM change (SE)	[redacted]	[redacted]		
	ppFEV$_1$ at screening ≥ 70%	n	[redacted]	[redacted]	[redacted]	[redacted]
		LSM change (SE)	[redacted]	[redacted]		
	ppFEV$_1$ at baseline < 40%	n	[redacted]	[redacted]	[redacted]	[redacted]
		LSM change (SE)	[redacted]	[redacted]		
	ppFEV$_1$ at baseline ≥ 40%	n	[redacted]	[redacted]	[redacted]	[redacted]
		LSM change (SE)	[redacted]	[redacted]		
TRANSPORT	Age ≥ 12 to < 18 years	n	[redacted]	[redacted]	[redacted]	[redacted]
		LSM change (SE)	[redacted]	[redacted]		
	Age ≥ 18 years	n	[redacted]	[redacted]	[redacted]	[redacted]
		LSM change (SE)	[redacted]	[redacted]		
	ppFEV$_1$ at screening < 70%	n	[redacted]	[redacted]	[redacted]	[redacted]
		LSM change (SE)	[redacted]	[redacted]		
	ppFEV$_1$ at screening ≥ 70%	n	[redacted]	[redacted]	[redacted]	[redacted]
		LSM change (SE)	[redacted]	[redacted]		
	ppFEV$_1$ at baseline < 40%	n	[redacted]	[redacted]	[redacted]	[redacted]
		LSM change (SE)	[redacted]	[redacted]		
	ppFEV$_1$ at baseline ≥ 40%	n	[redacted]	[redacted]	[redacted]	[redacted]
		LSM change (SE)	[redacted]	[redacted]		

CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; ppFEV$_1$ = per cent predicted forced expiratory volume in one second; SE = standard error; vs. = versus.

[a] Mixed-effects model for repeated measures included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 years versus ≥ 18 years), and ppFEV$_1$ severity at screening (< 70% versus ≥ 70%).[1,2]

Source: Clinical study reports.[1,2]

Table 34: Sensitivity Analyses for $ppFEV_1$ from TRAFFIC and TRANSPORT

Analysis	Study	Parameter	Placebo	L400/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; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; MMRM = mixed-effects model for repeated measures; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; SD = standard deviation; SE = standard error.

[a] Mixed-effects model for repeated measures included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex, age group at baseline (< 18 years versus ≥ 18 years), and $ppFEV_1$ at screening (< 70% versus ≥ 70%).

[b] ANCOVA model included treatment, sex, age at baseline (< 18 years versus ≥ 18 years), and $ppFEV_1$ at screening (< 70% versus ≥ 70%).

Source: Clinical study reports.[1,2]

Table 35: Subgroup Analyses for Absolute Change from Baseline in $LCI_{2.5}$

Study	Subgroup	Parameter	Placebo (N = 101)	L200/IVA (N = 103)	L200/IVA vs. Placebo	
					LSMD (95% CI)	*P* value
Study 109	$ppFEV_1$ at baseline < 90%	n	[redacted]	[redacted]	–1.08 (–1.61 to –0.54)	0.0001
		LSM change (SE)	[redacted]	[redacted]		
	$ppFEV_1$ at baseline ≥ 90%	n	[redacted]	[redacted]	–1.17 (–1.60 to –0.73)	< 0.0001
		LSM change (SE)	[redacted]	[redacted]		

CI = confidence interval; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; LCI = lung clearance index; LSM = least squares mean; LSMD = least squares mean difference; n = number of patients in the analysis; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; SE = standard error; vs. = versus.

Source: Clinical study report.[7]

Table 36: Subgroup Analyses for Pulmonary Exacerbations from TRAFFIC and TRANSPORT

Subgroup		End points	TRAFFIC		TRANSPORT	
			Placebo	L400/IVA	Placebo	L400/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; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; ppFEV$_1$ = per cent predicted forced expiratory volume in one second.

Note: Treatment comparison was carried out using regression analysis for a negative binomial distribution with sex (male versus female), age group (< 18 years old versus ≥ 18 years old), and ppFEV$_1$ at screening (< 70% versus ≥ 70%) as covariates with the logarithm of time on study as the offset.[1,2]

Source: Clinical study reports.[1,2]

Table 37: Change in CFQ-R (RD) at Each Study Visit in TRAFFIC and TRANSPORT

Time	Parameter	Placebo	L400/IVA	L400/IVA vs. Placebo	
				LSMD (95% CI)[a]	*P* value
TRAFFIC					
Baseline	n	184	181	–	–
	Mean (SD)	70.54 (16.032)	69.29 (17.424)		
Day 15	n	183	180	0.95 (–2.00 to 3.90)	0.5259
	LSM change (SE)	1.37 (1.088)	2.32 (1.096)		
	P value (within treatment)	0.2080	0.0344	–	–
Week 4	n	184	179	2.05 (–0.93 to 5.04)	0.1772
	LSM change (SE)	3.07 (1.097)	5.12 (1.109)		
	P value (within treatment)	0.0054	< 0.0001	–	–
Week 8	N	183	178	6.09 (2.84 to 9.35)	0.0003
	LSM change (SE)	–1.38 (1.191)	4.71 (1.205)		
	P value (within treatment)	0.2465	0.0001	–	–
Week 16	N	183	175	3.81 (0.74 to 6.89)	0.0152
	LSM change (SE)	0.72 (1.126)	4.53 (1.147)		
	P value (within treatment)	0.5239	< 0.0001	–	–
Week 24	N	184	172	1.50 (–1.69 to 4.69)	0.3569
	LSM change (SE)	1.10 (1.161)	2.60 (1.192)		
	P value (within treatment)	0.3423	0.0295	–	–

Time	Parameter	Placebo	L400/IVA	L400/IVA vs. Placebo	
				LSMD (95% CI)[a]	*P* value
TRANSPORT					
Baseline	n	187	185	–	–
	Mean (SD)	67.05 (18.394)	67.36 (18.540)		
Day 15	n	184	183	2.12 (–0.88 to 5.12)	0.1649
	LSM change (SE)	0.84 (1.114)	2.96 (1.117)		
	P value (within treatment)	0.4507	0.0083	–	–
Week 4	N	187	181	6.38 (3.42 to 9.34)	< 0.0001
	LSM change (SE)	1.04 (1.098)	7.42 (1.112)		
	P value (within treatment)	0.3449	< 0.0001	–	–
Week 8	N	185	182	5.29 (2.01 to 8.57)	0.0016
	LSM change (SE)	1.19 (1.209)	6.48 (1.218)		
	P value (within treatment)	0.3254	< 0.0001	–	–
Week 16	N	184	181	5.85 (2.56 to 9.15)	0.0005
	LSM change (SE)	0.14 (1.216)	6.00 (1.225)		
	P value (within treatment)	0.9069	< 0.0001	–	–
Week 24	N	185	179	2.85 (–0.27 to 5.98)	0.0736
	LSM change (SE)	2.81 (1.153)	5.66 (1.169)		
	P value (within treatment)	0.0152	< 0.0001	–	–

CFQ-R (RD) = Cystic Fibrosis Questionnaire – Revised (respiratory domain); CI = confidence interval; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; LSM = least squares mean; LSMD = least squares mean difference; SD = standard deviation; SE = standard error; vs. = versus.

Source: Clinical Study Reports[1,2]

Table 38: Change in CFQ-R (RD) at Each Study Visit in Study 109

Time	Parameter	Placebo	L400/IVA	L200/IVA vs. Placebo	
				LSMD (95% CI)[a]	*P* value
Children Aged Six to 11 Version					
Baseline	n	78	77	–	–
	Mean (SD)	77.1 (15.5)	78.7 (14.0)		
Day 15	n	78	76	4.1 (0.5 to 7.6)	0.0265
	LSM change (SE)	1.3 (1.3)	5.4 (1.4)		
	P value (within treatment)	0.3240	0.0001	–	–
Week 4	N	76	75	0.1 (–3.6 to 3.8)	0.9610
	LSM change (SE)	3.9 (1.4)	4.0 (1.4)		
	P value (within treatment)	0.0057	0.0056	–	–
Week 8	n	75	75	3.4 (–0.7 to 7.4)	0.0996
	LSM change (SE)	2.1 (1.5)	5.5 (1.5)		
	P value (within treatment)	0.1563	0.0004	–	–
Week 16	n	77	72	2.0 (–2.4 to 6.4)	0.3634
	LSM change (SE)	2.5 (1.6)	4.6 (1.6)		
	P value (within treatment)	0.1128	0.0064	–	–

Time	Parameter	Placebo	L400/IVA	L200/IVA vs. Placebo	
				LSMD (95% CI)[a]	*P* value
Week 24	n	75	73	2.9 (–0.7 to 6.6)	0.1170
	LSM change (SE)	5.2 (1.4)	8.1 (1.4)		
	P value (within treatment)	0.0002	< 0.0001	–	–
Through 24 weeks	n	78	76	2.5 (–0.1 to 5.1)	0.0628
	LSM change (SE)	3.0 (1.0)	5.5 (1.0)		
	P value (within treatment)	0.0035	< 0.0001		
Parents and Caregivers Version					
Baseline	n	100	103	–	–
	Mean (SD)	82.2 (15.3)	82.1 (14.9)		
Day 15	n	98	100	2.7 (–1.3 to 6.8)	0.1787
	LSM change (SE)	–2.3 (1.5)	0.5 (1.5)		
	P value (within treatment)	0.1248	0.7581	–	–
Week 4	n	95	101	–2.8 (–6.9 to 1.3)	0.1827
	LSM change (SE)	1.7 (1.5)	–1.1 (1.5)		
	P value (within treatment)	0.2771	0.4566	–	–
Week 8	n	96	99	2.3 (–2.0 to 6.6)	0.3000
	LSM change (SE)	–1.8 (1.6)	0.5 (1.6)		
	P value (within treatment)	0.2632	0.7612	–	–
Week 16	n	97	98	1.7 (–2.4 to 5.8)	0.4160
	LSM change (SE)	–1.4 (1.5)	0.3 (1.5)		
	P value (within treatment)	0.3625	0.8369	–	–
Week 24	n	96	98	2.6 (–1.4 to 6.5)	0.2038
	LSM change (SE)	1.0 (1.5)	3.6 (1.5)		
	P value (within treatment)	0.4790	0.0143	–	–
Through 24 weeks	n	99	102	1.3 (–1.2 to 3.8)	0.3022
	LSM change (SE)	–0.5 (1.0)	0.7 (0.9)		
	P value (within treatment)	0.5686	0.4314	–	–

CFQ-R (RD) = Cystic Fibrosis Questionnaire – Revised (respiratory domain); CI = confidence interval; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; LSM = least squares mean; LSMD = least squares mean difference; SD = standard deviation; SE = standard error; vs. = versus.

Source: Clinical study report.[7]

Table 39: Change in CFQ-R (RD) at Each Study Visit in Study 109

Time	Increase of ≥ 4 in CFQ-R (RD)	Placebo	L400/IVA	L400/IVA vs. Placebo	
				OR (95% CI)	*P* value
Study 109 (Patient Version)					
Day 15	Yes, n (%)	26 (25.7)	37 (35.9)	1.6209 (0.8870 to 2.9621)	0.1166
	No, n (%)	75 (74.3)	66 (64.1)		
Week 4	Yes, n (%)	33 (32.7)	33 (32.0)	0.9685 (0.5384 to 1.7422)	0.9157
	No, n (%)	68 (67.3)	70 (68.0)		
Week 8	Yes, n (%)	28 (27.7)	38 (36.9)	1.5079 (0.8365 to 2.7182)	0.1696
	No, n (%)	73 (72.3)	65 (63.1)		
Week 16	Yes, n (%)	35 (34.7)	35 (34.0)	0.9652 (0.5414 to 1.7207)	0.9051
	No, n (%)	66 (65.3)	68 (66.0)		
Week 24	Yes, n (%)	37 (36.6)	40 (38.8)	1.0858 (0.6141 to 1.9199)	0.7783
	No, n (%)	64 (63.4)	63 (61.2)		
Through 24 weeks	Yes, n (%)	32 (31.7)	34 (33.0)	1.0630 (0.5917 to 1.9096)	0.8386
	No, n (%)	69 (68.3)	69 (67.0)		
TRAFFIC (Pooled Patients and Caregiver Versions)					
Day 15	Yes, n (%)	64 (34.8)	79 (43.4)	1.4295 (0.9373 to 2.1801)	0.0976
	No, n (%)	120 (65.2)	103 (56.6)		
Week 4	Yes, n (%)	80 (43.5)	97 (53.3)	1.4803 (0.9795 to 2.2371)	0.0616
	No, n (%)	104 (56.5)	85 (46.7)		
Week 8	Yes, n (%)	65 (35.3)	90 (49.5)	1.7778 (1.1699 to 2.7016)	0.0071
	No, n (%)	119 (64.7)	92 (50.5)		
Week 16	Yes, n (%)	72 (39.1)	92 (50.5)	1.5930 (1.0478 to 2.4219)	0.0301
	No, n (%)	112 (60.9)	90 (49.5)		
Week 24	Yes, n (%)	83 (45.1)	85 (46.7)	1.0640 (0.7087 to 1.5975)	0.7628
	No, n (%)	101 (54.9)	97 (53.3)		
TRANSPORT (Pooled Patients and Caregiver Versions)					
Day 15	Yes, n (%)	69 (36.9)	79 (42.2)	1.2532 (0.8269 to 1.8992)	0.2890
	No, n (%)	118 (63.1)	108 (57.8)		
Week 4	Yes, n (%)	76 (40.6)	100 (53.5)	1.6908 (1.1166 to 2.5605)	0.0136
	No, n (%)	111 (59.4)	87 (46.5)		
Week 8	Yes, n (%)	70 (37.4)	93 (49.7)	1.6483 (1.0926 to 2.4866)	0.0174
	No, n (%)	117 (62.6)	94 (50.3)		
Week 16	Yes, n (%)	65 (34.8)	93 (49.7)	1.8535 (1.2222 to 2.8110)	0.0038
	No, n (%)	122 (65.2)	94 (50.3)		
Week 24	Yes, n (%)	76 (40.6)	84 (44.9)	1.1902 (0.7877 to 1.7983)	0.4107
	No, n (%)	111 (59.4)	103 (55.1)		

CFQ-R (RD) = Cystic Fibrosis Questionnaire – Revised (respiratory domain); CI = confidence interval; lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; OR = odds ratio; vs. = versus.

Source: Clinical study report.[7]

Table 40: Changes in BMI, Weight, and Height from Study 11B

	BMI (kg/m^2)	BMI-for-age z score	Weight (kg)	Weight-for-age z score	Height (cm)	Height-for-age z score
Baseline						
n	58	58	58	58	58	58
Mean (SD)	16.89 (1.93)	0.01 (0.90)	31.5 (6.1)	–0.03 (1.03)	136.2 (8.6)	0.03 (1.08)
Absolute Change at Day 15						
n	57	57	57	57	57	57
LS mean (95% CI)	0.09 (0.00 to 0.17)	0.04 (–0.01 to 0.09)	0.2 (0.0 to 0.4)	0.02 (–0.01 to 0.06)	0.2 (0.0 to 0.3)	–0.01 (–0.03 to 0.02)
P value within treatment	0.0578	0.1460	0.0179	0.2286	0.0535	0.4831
Absolute Change at Week 4						
n	56	56	56	56	56	56
LS mean (95% CI)	0.12 (0.02 to 0.23)	0.07 (0.01 to 0.12)	0.4 (0.3 to 0.6)	0.05 (0.01 to 0.08)	0.5 (0.3 to 0.7)	0.01 (–0.02 to 0.05)
P value within treatment	0.0197	0.0151	< 0.0001	0.0113	0.0001	0.4920
Absolute Change at Week 8						
n	56	56	56	56	56	56
LS mean (95% CI)	0.25 (0.11 to 0.40)	0.08 (0.01 to 0.15)	0.9 (0.7 to 1.2)	0.07 (0.02 to 0.11)	1.0 (0.7 to 1.2)	0.02 (–0.02 to 0.06)
P value within treatment	0.0008	0.0205	< 0.0001	0.0057	< 0.0001	0.3483
Absolute Change at Week 16						
n	56	56	56	56	56	56
LS mean (95% CI)	0.40 (0.23 to 0.57)	0.11 (0.04 to 0.19)	1.6 (1.2 to 2.0)	0.08 (0.02 to 0.14)	1.8 (1.5 to 2.1)	0.01 (–0.04 to 0.05)
P value within treatment	< 0.0001	0.0043	< 0.0001	0.0111	< 0.0001	0.7654
Absolute Change at Week 24						
n	56	56	56	56	56	56
LS mean (95% CI)	0.64 (0.46 to 0.83)	0.15 (0.08 to 0.22)	2.6 (2.2 to 3.0)	0.13 (0.07 to 0.19)	2.9 (2.6 to 3.2)	0.03 (–0.02 to 0.09)
P value within treatment	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.2249

BMI = body mass index; CI = confidence interval; LS = least squares; SD = standard deviation.

Source: Clinical study report.[6]

Table 41: Summary of Adverse Events from TRAFFIC and TRANSPORT

Adverse Events, n (%)	TRAFFIC		TRANSPORT	
	Placebo	L400/IVA	Placebo	L400/IVA
Summary of Adverse Events				
Any adverse events	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 Adverse Events (≥ 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)
Abnormal respiration	9 (4.9)	14 (7.7)	13 (7.0)	18 (9.6)
Increased sputum	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)
Withdrawals Due to Adverse Events				
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/ivacaftor 250 mg every 12 hours; WDAE = withdrawals due to adverse event.

Sources: Wainwright et al., 2015,[3] Common Technical Document section 2.7.4,[4] and Clinical study reports for TRAFFIC[1] and TRANSPORT.[2]

Table 42: Respiratory Adverse Events by FEV_1 at Baseline (A) or Screening (B)

A: [redacted]

Preferred Term, n (%)	[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]

L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; $ppFEV_1$ = per cent predicted forced expiratory volume in one second.

Source: Common Technical Document section 2.7.4.[4]

B: [redacted]

Preferred Term, n (%)	[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]

L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; $ppFEV_1$ = per cent predicted forced expiratory volume in one second.

Source: Common Technical Document section 2.7.4.[4]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe and critically appraise the following outcome measures:

- forced expiratory volume in one second (FEV_1)
- lung clearance index (LCI)
- Cystic Fibrosis Questionnaire – Revised (CFQ-R)
- EuroQol 5-Dimensions 3-Level questionnaire (EQ-5D-3L).

Table 43: Summary of Appraisal of Outcome Measures

Instrument	Type	Conclusions about Measurement Properties	MCID
FEV_1	Pulmonary function test (maximal amount of air forcefully exhaled in one second)	FEV_1 has been shown to relate to morbidity, disease progression, and mortality in CF, and thus is a meaningful surrogate marker for survival. FEV_1 is highly dependent on patient cooperation and effort to perform test and can only be used on children old enough to comprehend and follow the instructions given. It has a ceiling effect for patients with mild lung impairment.	Not defined
LCI	Pulmonary function test (the number of lung volume turnovers required to clear the lung of an inert gas)	LCI has shown discriminant validity for known groups; however, it is not known if LCI is predictive of longer-term changes in health status. Variable correlation was observed between FEV_1 and LCI in children. Measurements using different LCI systems are not interchangeable and further testing standardization is required. Limited longitudinal data are available to understand how LCI changes by age, sex, or ethnic group.	Not defined
CFQ-R Respiratory	Respiratory symptom scale of a disease-specific HRQoL instrument	Internal consistency reliability acceptable. Showed discriminant validity for sick versus well patients with CF, and moderate correlation with FEV_1. Responsiveness to change in lung function or exacerbations has been shown in clinical trials for various CF treatments.	Stable CF: 4.0 points; exacerbation of CF: 8.5 points
EQ-5D-3L	Generic, preference-based measure of HRQoL	Measurement properties not assessed in CF.	Index score: 0.033 to 0.074 for general use

CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire – Revised; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; FEV_1 = forced expiratory volume in one second; HRQoL = health-related quality of life; LCI = lung clearance index; MCID = minimal clinically important difference.

Findings

Forced Expiratory Volume in One Second

FEV_1 is the maximal amount of air forcefully exhaled in one second, expressed in litres.[100] The measured volume is converted to a percentage of predicted normal value, which is adjusted based on age, sex, and body composition.[100] 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).[100,101]

FEV_1 is a commonly used end point for clinical trials of obstructive lung diseases including CF[102] and is the preferred end point in the European Medicines Agency guidance document on the development of therapeutic drugs for CF, based on the fact that the main pulmonary defect in CF is obstructive.[101] FEV_1 has been shown to relate to morbidity, disease progression, and mortality in CF, making it a meaningful surrogate marker for survival.[102]

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

- The maneuver 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[100]
  - spirometry can only be used 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[101,102]
  - 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.[102]
- There are no published data on the magnitude of change in FEV_1 that is clinically meaningful.[102]
- CF is a multi-organ disease and FEV_1 only measures lung health.[102]
- FEV_1 improvement has a ceiling effect for patients with mild lung impairment.[102]
- There are no published minimal clinically important differences (MCID) for FEV_1 in patients with CF.[48]

The European Medicines Agency 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.[101]

Lung Clearance Index

The LCI is a measure of overall lung ventilation inhomogeneity.[46] This multiple-breath washout test estimates the number of lung volume turnovers required to clear the lung of an inert gas. The test is sensitive to changes in the small airways, and may be able to detect pulmonary disease in patients with normal FEV_1.[47,48] Several commercial and research-specific multiple-breath washout devices have been developed. These devices include a patient interface (i.e., face mask), flow metre, gas analyzer or mass spectrometer (to analyze gas concentrations), and a gas delivery system.[103] Software is required to analyze the results, and quality assurance testing is needed to ensure the performance of the test was satisfactory (i.e., within-session reproducibility).[103] The test may use an extrinsic inert gas, such as sulphur hexafluoride or helium, or an intrinsic gas, such as nitrogen. During the wash-in phase for an extrinsic gas test, the patient inhales the test gas until the

delivered gas concentrations and the exhaled concentration are equal. In the washout phase, the patient inhales room air and continues normal tidal breathing until the exhalation concentration of the gas falls to 1/40th ($LCI_{2.5}$) or 1/20th (LCI_5) of the wash-in concentration. For the test using nitrogen, there is no wash-in phase as the concentration of nitrogen is normally at 80%. During the washout phase the patient inhales 100% oxygen until nitrogen levels fall to 1/40th or 1/20th of initial values. As ventilation worsens the number of tidal breaths and expired volumes required to clear the gas increases, thus higher LCI values indicate greater ventilation inhomogeneity. The LCI is calculated as the mean of two or three tests that meet acceptable performance standards (e.g., functional residual capacity values within 10%). In 2012, the European Respiratory Society and the American Thoracic Society published guidelines for washout equipment specifications, test performance and analysis, and outlined essential principles of multiple-breath washout testing.[103]

Kent et al.[47] conducted a review of the evidence for the use of LCI in clinical trials in patients with CF. These studies were conducted predominantly in children, and most were cross-sectional studies that were completed prior to the European Respiratory Society and American Thoracic Society guidelines for LCI testing were published. LCI was able to discriminate between patients with CF and healthy individuals in 22 out of 23 studies reviewed. Variable correlation was observed between FEV_1 and LCI among 10 studies in children, and moderate-to-strong correlation was found between LCI and various structural abnormalities observed in high resolution computed tomography (Spearman correlation coefficient range 0.31 to 0.77; five studies).[47] LCI detected treatment effects after four weeks of inhaled dornase alpha or hypertonic saline, and after a course of intravenous (IV) antibiotics in patients with an exacerbation or colonized with *Pseudomonas aeruginosa*.[47,104] In contrast, another study found no statistically significant difference in LCI at admission and at discharge among 27 school-aged children hospitalized to receive IV antibiotics for a pulmonary exacerbation of CF.[105]

In a single-centre study by Vermeulen et al.,[106] LCI z scores were negatively correlated with FEV_1 z scores (Spearman correlation coefficient r: –0.642) and CRQ-R respiratory score (r: –0.431) in children aged five years to 20 years with CF (N = 63, mean LCI 10.8 [standard deviation: 3.1] Exhalyzer D nitrogen device).[106] Of the 53 patients with a normal FEV_1, 42 (79%) had an abnormal LCI (defined as a z score > 2). Time-to-first pulmonary exacerbation (defined as change in respiratory status that was treated with IV antibiotics) decreased with worsening LCI quartiles (log rank test $P < 0.001$), FEV_1 z score quartiles ($P = 0.002$) and CFQ-R respiratory quartiles ($P = 0.001$) over the one-year follow-up.[106] Another study that examined the change in lung function over one year in healthy preschool children (N = 78) and those with CF (N = 78) found that $ppFEV_1$ and LCI were able to discriminate between groups.[107] LCI also showed an increase over time (i.e., worsening) in patients with CF compared with stable LCI in healthy age-matched children.[107]

Kent et al.[47] reported inter-test repeatability in children with CF, and found variability of 0.96 units of LCI (coefficient of repeatability), and 2.6% to 9.2% (coefficient of variation) for tests performed 1.5 hours to 12 weeks apart (patient demographics not reported).[47] Oude Engberink et al.[108] evaluated the inter-test reproducibility of the LCI in healthy preschool children and children with stable CF who were aged 2.5 years to 6 years. Repeated measures of LCI were obtained using the Exhalyzer D device, one month to three months apart over one year, and inter-visit reproducibility was calculated using several methods (Table 44). The authors stated that interpretation of the LCI in terms of an absolute change was prone to bias, as a key assumption for Bland-Altman limits of agreement or coefficient of repeatability was not met. Use of the results of these tests, which suggested a 1-unit

change in healthy children would be clinically meaningful, would lead to an over-estimation of clinically relevant changes in patients with higher LCI values.[108] The authors concluded that repeated measures of the LCI should be interpreted as a percentage change, and ± 15% represents physiologically relevant change that is greater than biologic variability of the test.[108]

Table 44: Inter-Test Reproducibility of the Lung Clearance Index in Preschool Children

	Healthy	Stable CF
N	71	77
Median LCI (range) at baseline	7.1 (6.1 to 8.1)	8.9 (6.40 to 16.2)
Measures of reproducibility for LCI		
Absolute mean difference	–0.03	–0.05
Percentage change (95% limits)	–0.14 (–15 to 15)	1.27 (–25 to 27)
Per cent coefficient of variation	4.3%	7.7%
ICC	0.4	0.7
Bland-Altman limits of agreement[a]	–1.1 to 1.1	–2.9 to 2.8
Coefficient of repeatability[a]	0.9	2.0

CF = cystic fibrosis; ICC = intra-class correlation coefficient; LCI = lung clearance index.

[a] Test assumes the within-patient standard deviation is proportional to the magnitude of the measurement, which was not met for the LCI in healthy children or those with CF.

Source: Oude Engberink et al.[108]

Poncin et al.[109] found that the agreement between two commercial nitrogen multiple-breath washout devices was poor, with the Exhalyzer D measuring higher LCI values than the EasyOne Pro device in adults and children with CF (N = 104) and those without CF (N = 101). The difference was deemed to be clinically relevant as it exceeded the anticipated magnitude of the between-test variability (10%).[109] Thus, there may be issues with comparing LCI results between clinical trials.

The feasibility of the LCI was estimated from the percentage of patients who could successfully complete one to three LCI tests within a session. Based on data from 19 patient groups (infants to adults), 24% to 100% of patients were able to successfully complete the LCI test.[47] Grosse-Onnebrink et al.[110] found that chest physiotherapy can have a short-term impact on LCI, potentially biasing results, and therefore the timing of physiotherapy in relation to LCI should be considered in clinical trials.

Limitations

- Measurements using different inert gases, devices, or analytical software are not interchangeable and thus normative data from one system cannot be used for other devices.[46] Standardization of procedures is required in order to compare results between studies.[103]
- The MCID has not been defined. Limited longitudinal data are available to understand how ventilation inhomogeneity indices change during normal lung development, by age, sex, or ethnic group.[46,103] These data are required to define whether an intervention exceeds the intrinsic variability of the test.[48]
- It is unclear if improvement in LCI is predictive of longer-term changes in health status, such as the change in FEV_1 or frequency of exacerbations.[46]

- Several procedural specific issues require further evaluation. Some examples include defining the optimal washout cut off value (i.e., 1/40th or 1/20th of initial gas concentration), the number of repeated tests required to ensure accurate results, and impact of sedation on breathing pattern and LCI in infants or young children.[103]
- The test has less potential for use in trials in patients with advanced lung disease due to the long measurement times and greater variability.[48]

Cystic Fibrosis Questionnaire – Revised

The CFQ-R is a disease-specific quality of life (QoL) instrument designed for patients with CF, comprised of age-appropriate versions for children aged six to 13 (CFQ-C) and their parents (who serve as a proxy for their child; CFQ-P), and individuals ≥ 14 years of age (CFQ-14).[111] The number of items and domains vary between versions with the child version including 35 items within eight domains, the parent version has 44 items and 11 domains, and the adult version has 48 items within 12 domain.[112,113] The domains included in the adult version are as follows: QoL module including physical functioning, vitality, emotional functioning, social functioning, role limitations, body image, eating disturbances, treatment burden; symptoms module including respiratory symptoms, digestive symptoms, and weight; and a health perception module. Items within domains are summed 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.[114]

Several studies have evaluated the validity and reliability of the CFQ-R questionnaire.[113,115,116] Quittner et al.[113] 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 years to 70 years, plus data from 2,728 parents for the CFQ-P. Quittner et al.[113] reported adequate internal consistency (Cronbach alpha ≥ 0.70) for most domains and scales on each of the three versions, with lower reliability (< 0.6) found for treatment burden, social functioning, or school functioning. For the respiratory symptom domain, the Cronbach alpha reported was 0.87, 0.69, 0.82 for the CRQ-14, CFQ-C, and CFQ-P, respectively.[113] Discriminant validity was demonstrated as CFQ scores were consistently lower for patients who were sick, compared with those who were well for all three versions of the instrument.[113] For the respiratory domain specifically, the effect size for the difference in mean scores ranged from –0.59 to –0.95 across the three versions.[113]

The most CFQ domains were sensitive to changes in QoL associated with increasing disease severity (based on pulmonary function, FEV_1); this analysis was limited, however, since the CFQ-C had less variability in disease severity as few school-age children had a FEV_1 < 70% predicted.[113] The respiratory domain is reported to have demonstrated appropriate changes where lung function or exacerbation changes have occurred, such as in trials for inhaled antibiotics, hypertonic saline, IVF, and other treatments.[48] There was fair-to-moderate convergence between CFQ-R scales and health outcomes, including per cent predicted FEV_1 (correlation range, 0.25 to 0.51), number of pulmonary exacerbations treated with IV antibiotics (range: −0.23 to −0.35), and BMI (range: 0.22 to 0.44). The strongest correlations were demonstrated for the physical functioning and respiratory domains with per cent predicted FEV_1 (range: 0.33 to 0.51 and 0.32 to 0.42, respectively) and for the weight scale and BMI (range: 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 than the CFQ-14. Test-retest reliability was assessed previously (repeat administration over 14 days) and

intra-class correlation coefficients were estimated to range from 0.45 to 0.90 on all scales.[115]

Quittner et al.[113] also reported fair-to-moderate agreement between the child and parent versions on all scales (intra-class 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. Tluczek et al.[112] examined parent-child concordance in CFQ-R domains for children aged eight years to 13 years and adolescents aged 14 years to 18 years (total N = 92 pairs). Five of the domains of the CFQ-C instrument were similar to the parent-reported CFQ-14, with children reporting better health-related QoL (HRQoL) than parents for the digestive symptoms and body image domains.[112] Male children reported worse HRQoL on emotional functioning that their parents. Adolescents rated HRQoL higher than their parents on weight, body image, digestive symptoms, eating disturbance, physical and emotional functioning, treatment burden, and respiratory symptoms.[112] Many of the differences were driven by male adolescents.[112]

A study[115] also showed the CFQ-R correlated well with the SF-36. Correlations were moderate to strong (range: 0.42 to 0.57) between similar dimensions of the CFQ and SF-36 (physical, health perceptions and general health, vitality, role/role physical, emotional functioning and mental health, and social) and weak to moderate (range: 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 for the CFQ-R respiratory symptom scale in two study populations: one with patients with stable CF and chronic *P. aeruginosa* airway infection (N = 140); the other with patients with exacerbation of CF and chronic *P. aeruginosa* airway infection (N = 84).[49] Both anchor-based and distribution-based methods were used. The anchor-based methods used a Global Rating of Change Questionnaire that assessed patients' perceptions of the change in their respiratory symptoms. The MCID for patients with stable disease was estimated to be 4.0 points, and for patients with exacerbation, 8.5 points.[49] The MCID values based on distribution methods (0.5 standard deviation of mean change in scores or 1 standard error of the mean for baseline scores) showed similar results for the stable patients (MCID 6.2 and 6.1) and those with an exacerbation (9.6 and 10.1).[49]

The main limitations of the CFQ-R are ceiling effects for certain scales (notably the eating and weight scale for the CFQ-14, eating, digestion, and body image for CFQ-C; and eating, weight, body image, and school functioning for CFQ-P), 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").[102,113]

EuroQol 5-Dimensions Questionnaire

The EQ-5D[117,118] 3-Levels 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-3L 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.[117,118] 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-3L 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-3L index score ranges from 0.033 to 0.074 for general use.[50] The validity, reliability, responsiveness, and MCID of the EQ-5D have not been formally assessed in CF.

Appendix 5: Summary of Study 106 (Advanced Lung Disease)

The objective of this appendix is to provide a summary and critical appraisal of Study 106, which evaluated the safety and tolerability of lumacaftor 400 mg/ivacaftor 250 mg every 12 hours (L400/IVA) in patients aged 12 years and older with cystic fibrosis (CF) homozygous for the F508del-cystic fibrosis transmembrane conductance regulator (CFTR) mutation.

Study Design

Study 106 was a prospective, open-label, single-arm clinical trial in patients (N = 46) who were 12 years of age or older with CF homozygous for F508del-CFTR mutation and with advanced lung disease (defined as per cent predicted forced expiratory volume in one second [$ppFEV_1$] < 40). All patients received L400/IVA for up to 24 weeks.

Outcomes

The primary objective was to determine the safety and tolerability of lumacaftor/ivacaftor (LUM/IVA). Efficacy was assessed as a the secondary objective and included the following outcome measures: absolute change from baseline in $ppFEV_1$, change from baseline in FEV_1 (L), days of intravenous (IV) antibiotics for sinopulmonary signs and symptoms, hospitalizations, change in sweat chloride, and change from baseline in Cystic Fibrosis Questionnaire – Revised (CFQ-R) respiratory domain.

The change from baseline efficacy outcomes were analyzed at each visit up to week 24 using a mixed-effect model for repeated measures (MMRM) that included the change from baseline in the outcome (e.g., $ppFEV_1$, CFQ-R) as the dependent variable, visit as a fixed effect, and subject as a random effect, with adjustment for sex, and baseline outcome measure (as continuous variables). All measurements up to 24 weeks were included in the model, even if the patient had discontinued treatment.

The total days of IV antibiotics was adjusted for the patient's time in the study by multiplying the observed per cent days with the event by the total study days expected through to week 24 (i.e., 168 days). The total number of days of IV antibiotics in the 24 weeks prior to enrolment was also calculated and was compared with the on-treatment days using a paired sample t-test. If the normality assumption was violated, a Wilcoxon signed rank test was used instead.

Regression analysis of the number of all-cause hospitalizations was conducted using a negative binomial distribution with sex as a covariate and the log of time in the study as the offset. The primary result of the model was the annualized number of all-cause hospitalizations. Hospitalizations in the 24 weeks prior to enrolment were estimated using the same methods. The number of hospitalizations on study was compared with the 24 week prior to enrolment based on a paired sample t-test. If the normality assumption was violated a Wilcoxon signed-rand test was used instead.

All efficacy evaluations included outcome data while on treatment and events after treatment discontinuation, up to study week 24. There was no imputation of missing data for the efficacy outcomes and no multiplicity adjustment for statistical testing.

Patient Disposition

The study planned to enrol between 100 patients and 200 patients; however, only 46 patients participated (enrolled from six US sites). The manufacturer stated this was likely due to the availability of commercial LUM/IVA. Of these patients, 18 (39%) received a reduced initial dose of LUM 200 mg/IVA 125 mg every 12 hours for the first week. Thirty-five patients (76%) completed 24 weeks of treatment, and 33 patients (72%) completed the study. The most common reason for discontinuing was adverse events (AEs), which were reported in 13% of patients (Table 45). The median duration of exposure was 168 days (range: 1 to 181; mean: 146 days).

Table 45: Patient Disposition in Study 106

Category	L400/IVA (N = 46)
Enrolled, N	46
Discontinued study, n (%)	13 (28)
Adverse events	6 (13)
Withdrawal of consent	1 (2)
Lost to follow-up	2 (4)
Death	1 (2)
Physician decision	1 (2)
Other	2 (4)
Full analysis set	46
Safety set	46

LUM 400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours.

Source: Clinical study report.[28]

Baseline Characteristics

The average age of patients enrolled was 32 years (standard deviation [SD]: 9.0), of which 65% were male and all were white (Table 46). The mean $ppFEV_1$ at baseline was 29 (SD: 5.1), and two patients were on the wait-list for a lung transplant.

Table 46: Baseline Characteristics in Study 106

Category	LUM 400/IVA (N = 46)
Female, n (%)	16 (35)
Age (years)	
Mean (SD)	32.1 (9.0)
12 to < 18	1 (2)
≥ 18	45 (98)
White, n (%)	46 (100)
Weight kg, mean (SD)	62.3 (13.1)
BMI kg/m^2, mean (SD)	21.4 (2.9)
ppFEV$_1$	
Mean (SD)	29.1 (5.1)
Range	18.3, 42.0
< 40	45 (98)
≥ 40	1 (2)
FEV$_1$ (L)	
Mean (SD)	1.12 (0.28)
On lung transplant wait-list at screening, n (%)	2 (7)
Prior medications for CF	
Dornase alfa	38 (83)
Inhaled hypertonic saline	36 (78)
Inhaled antibiotic	39 (85)
Any bronchodilator	45 (98)

BMI = body mass index; CF = cystic fibrosis; FEV$_1$= forced expiratory volume in one second; LUM 400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; ppFEV$_1$= per cent predicted forced expiratory volume in one second; SD = standard deviation.

Source: Clinical study report.[28]

Adverse Events

Most patients (94%) experienced an AE during the 24 week study period (Table 47). Infective pulmonary exacerbations (59%), abnormal respiration (57%), cough (46%), and dyspnea (44%) were the most frequently reported events. Eight patients (17%) stopped treatment due to AEs, including respiration abnormal (three patients) and dyspnea or dyspnea exertional (three patients). One patient died due to a serious adverse event (SAE) of hemoptysis on day 16. The patient had received LUM/IVA for four days and discontinued treatment due to chest tightness. Overall, 18 patients (39%) experienced one or more SAEs, of which infective pulmonary exacerbation of CF was the most commonly reported (16 patients, 35%). All other SAEs occurred in one patient (bacteremia, influenza, pneumonia, cough, hemoptysis, abnormal respiration, pyrexia, arthralgia, and neuralgia).

Table 47: Adverse Events from Study 106

Adverse Events	L400/IVA (N = 46)
Any adverse events, n (%)	43 (94)
Infective pulmonary exacerbation of CF	27 (59)
Abnormal respiration	26 (57)
Cough	21 (46)
Dyspnea	20 (44)
Increased sputum	13 (28)
Withdrawals due to adverse events	8 (17)
Serious adverse events	18 (39)
Deaths	1 (2)
Notable harms	
Elevated transaminases	3 (7)
Respiratory-related adverse events[a]	30 (65)
Cataracts	NR

CF = cystic fibrosis; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; NR = not reported

[a] Included asthma, bronchial hyperreactivity, bronchospasm, chest discomfort, dyspnea, abnormal respiration, and wheezing.

Source: Clinical study report.[28]

Efficacy

Efficacy end points in Study 106 are summarized in Table 48.

Table 48: Summary of Efficacy Outcomes in Study 106

Outcome	Study 106 (FAS)	
	N	LUM 400/IVA (N = 46)
$ppFEV_1$ (%)		
Baseline (SD)	46	29.1 (5.1)
Absolute change at week 24, LS mean (95% CI)[a]	32	–0.4 (–1.9 to 1.1)
P value within treatment		0.62
Responder Analysis		
≥ 3% increase in $ppFEV_1$ at week 24, n (%)	46	8 (17)
≥ 5% increase in $ppFEV_1$ at week 24, n (%)		3 (7)
≥ 10%increase in $ppFEV_1$ at week 24, n (%)		1 (2)
CFQ-R Respiratory Domain		
Baseline (SD)	46	52.5 (21.8)
Average absolute change through week 24, LS mean (95% CI)[a]	44	2.5 (–1.0 to 5.9)
P value within treatment		0.16
BMI (kg/m^2)		
Baseline (SD)	46	21.4 (2.9)
Absolute change at week 24, LS mean (SD)	35	0.29 (1.0)
P value within treatment		NR
Normalized Total Duration of IV Antibiotics (Days)		
24 weeks on study, mean (SD)	46	11.4 (18.2)
24 weeks prior to study, mean (SD)		19.9 (25.9)

Outcome	Study 106 (FAS)	
	N	LUM 400/IVA (N = 46)
Mean difference (SD) on study versus prior to study		–8.5 (24.9)
P value[b]		0.037
Number of Hospitalizations (All-Cause)		
Event rate per year (95% CI) on study	46	1.14 (0.70 to 1.84)
Event rate per year (95% CI) prior to study		2.87 (1.74 to 4.74)
P value[b]		0.0002

BMI = body mass index; CI = confidence interval; CFQ-R = Cystic Fibrosis Questionnaire – Revised; FAS = full analysis set; IV = intravenous; LS = least squares; LUM 400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; NR = not reported; $ppFEV_1$ = per cent predicted forced expiry volume in 1 second; SD = standard deviation.

[a] Mixed-effects model for repeated measures.

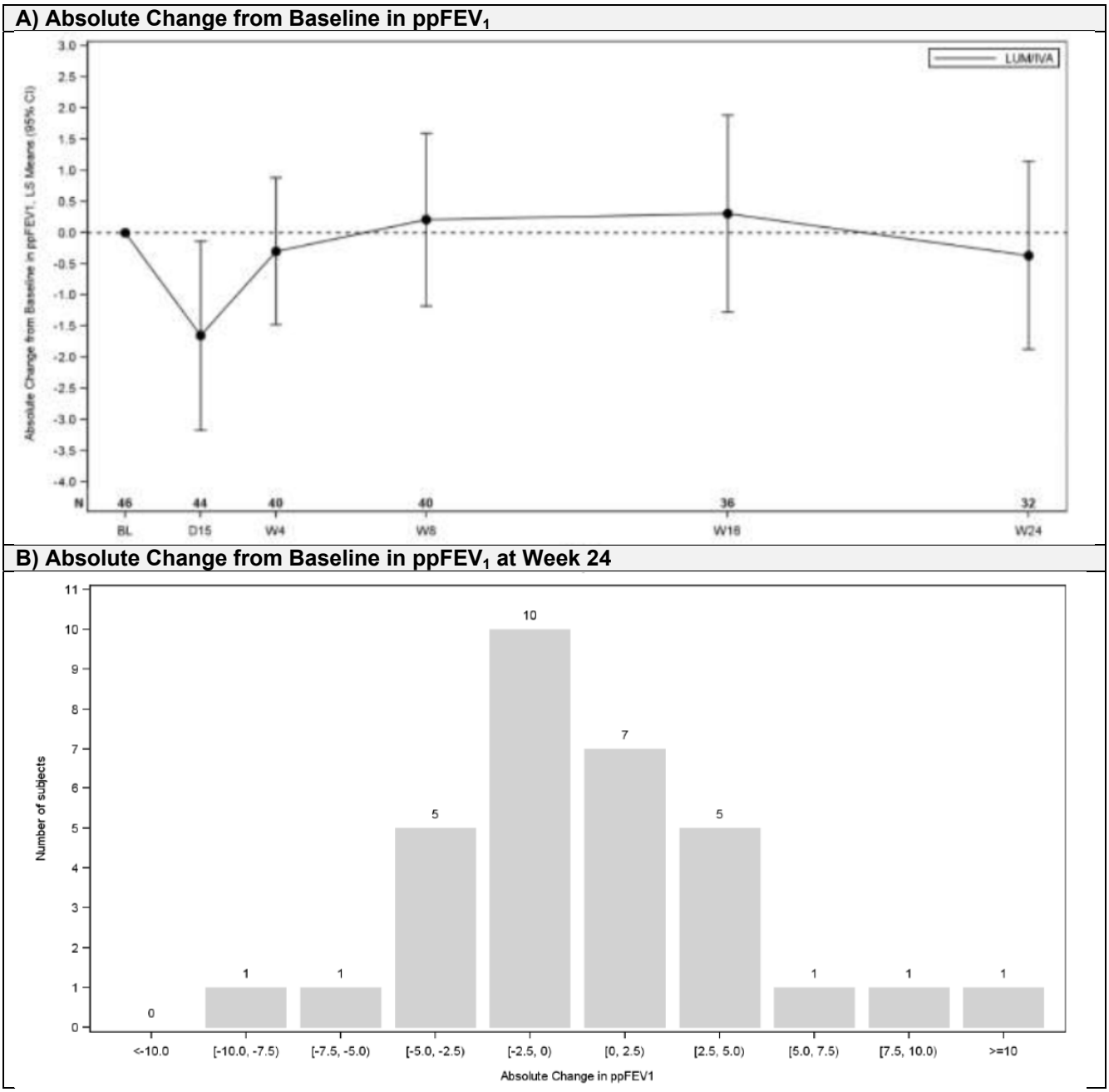
[b] Wilcoxon signed rank test.

Source: Clinical study report.[28]

Forced Expiratory Volume in One Second

At baseline the mean $ppFEV_1$ was 29.1% (SD: 5.1) and showed an initial decrease from baseline (at day 15), but was similar to baseline at weeks 4, 8, 16, and 24 (Figure 11). The least squares mean change from baseline to week 24 in the $ppFEV_1$ was –0.4 (95% confidence interval [CI], –1.9 to 1.1) based on the MMRM analysis. Three patients (7%) had an absolute increase in $ppFEV_1$ of 5% or greater at week 24 (Figure 11). Of note, data were missing from 4% of patients (at day 15) to 30% of patients (at week 24) for this outcome measure.

Figure 11: Absolute Change from Baseline in ppFEV$_1$ in Study 106



BL = baseline; CI = confidence interval; D = day; LUM/IVA = lumacaftor/ivacaftor; LS = least squares; ppFEV$_1$ = per cent predicted forced expiratory volume in one second; W = week.

Source: Clinical study report.[28]

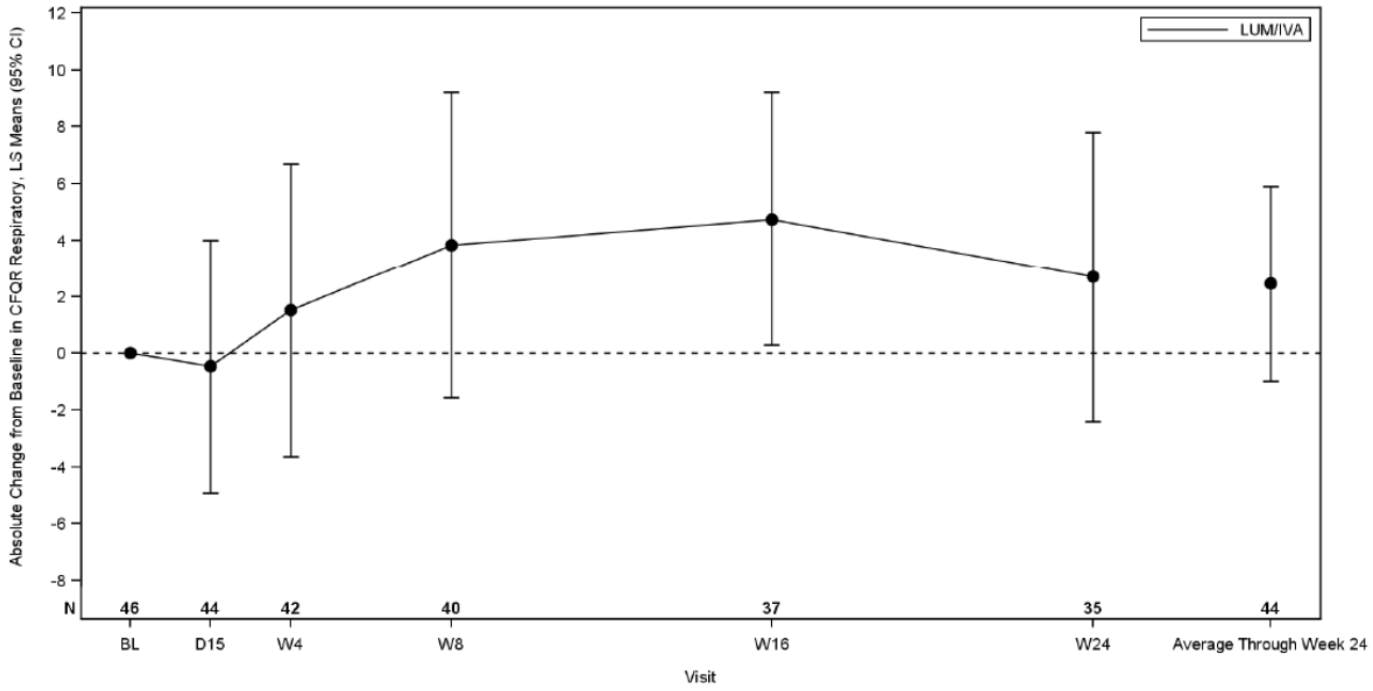
Hospitalization and Intravenous Antibiotics

In Study 106, 22 patients (48%) received 34 courses of antibiotics during the 24-week study period. The mean normalized total duration of IV antibiotics for sinopulmonary signs and symptoms was 11.4 days (SD: 18.2; range: 0 to 83). This was compared with the 24-week period prior to the study, during which a mean of 19.9 days (SD: 25.9; range: 0 to 119) of IV antibiotics was received by 28 patients. During the 24-week study period, 16 patients (35%) were hospitalized for any cause (in a total of 23 hospitalizations), for an annual event rate of 1.14 (95% CI, 0.70 to 1.84). Based on the 24 weeks prior to enrolment, the annual hospitalization rate was 2.87 (95% CI, 1.74 to 4.74).

Cystic Fibrosis Questionnaire – Revised

The mean CFQ-R respiratory domain score was 52.5 (SD: 21.8) at baseline and the least squares mean change over 24 weeks was 2.5 (95% CI, –1.0 to 5.9), based on the MMRM analysis. The mean baseline BMI was 21.4 kg/m^2 (SD: 2.9) and the mean change from baseline to week 24 was 0.3 (SD: 1.0). Data were missing from 4% (day 15) to 24% of patients (week 24) for these outcome measures.

Figure 12: Absolute Change from Baseline in CFQ-R Respiratory Domain in Study 106

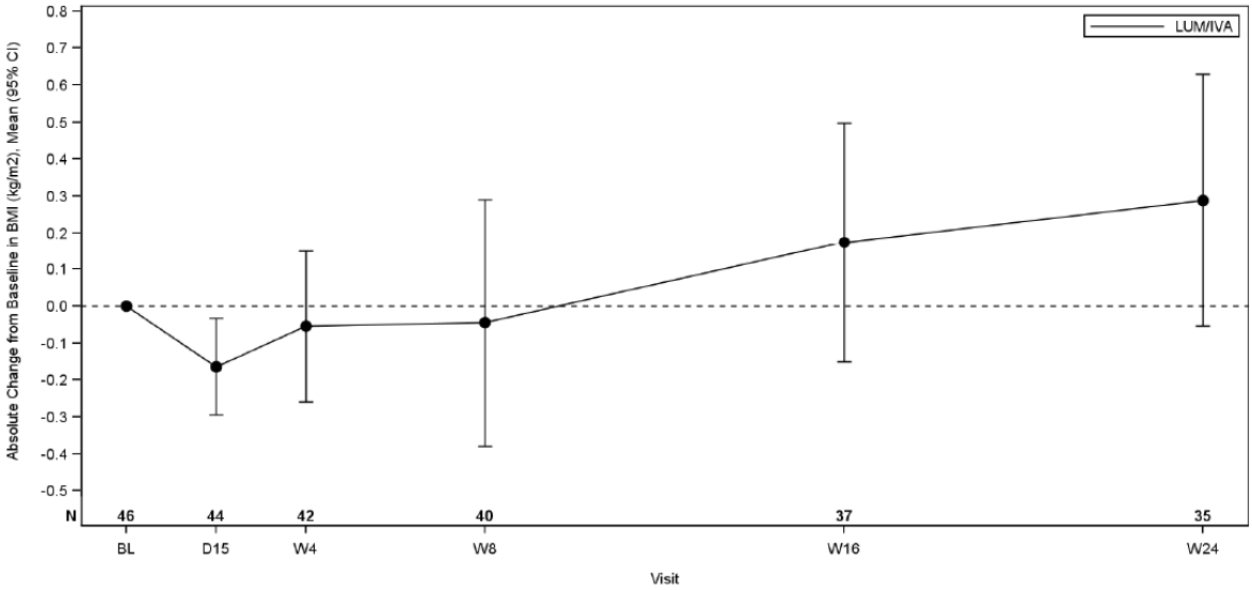


BL = baseline; CFQ-R = Cystic Fibrosis Questionnaire – Revised; CI = confidence interval; D = day; LS = least squares; LUM/IVA = lumacaftor/ivacaftor; W = week.
Source: Clinical study report.[28]

Body Mass Index

The mean baseline body mass index was 21.4 kg/m^2 (SD: 2.9) and the mean change from baseline to week 24 was 0.3 kg/m^2 (SD: 1.0). Data were missing from 4% (day 15) to 24% of patients (week 24) for these outcome measures.

Figure 13: Absolute Change from Baseline in BMI from Study 106



BL = baseline; BMI = body mass index; CI = confidence interval; D = day; LUM/IVA = lumacaftor/ivacaftor; W = week.

Source: Clinical study report.[28]

Limitations

The study was limited by the lack of a concurrent control group, small sample size (46 patients), and open-label design (potential for bias with subjective outcomes, such as CFQ-R, or reporting of harms). Moreover, data were missing from 4% to 30% of patients for different outcomes and time points. These data are unlikely to be missing at random, and may be associated with outcomes. In general, patients who are sicker may be more likely to be missing, which could bias the findings. The methods used to collect and validate the retrospective data on antibiotic use and hospitalizations were not specified. The comparisons between on-study use of IV antibiotics and hospitalizations with data gathered retrospectively prior to enrolment may be potentially confounded due to differences in data collection methods, seasonality, or other factors; therefore, these data should be interpreted with caution. Numerous statistical tests were performed without any control for multiplicity; thus, there is an inflated risk of type I error. The duration of treatment was 24 weeks, so it is not possible to assess longer-term safety of L400/IVA in this patient population.

Summary

Study 106 was a prospective, open-label, uncontrolled clinical trial in patients (N = 46) who were 12 years of age or older with CF homozygous for F508del-CFTR mutation and with advanced lung disease (defined as $ppFEV_1 < 40$). Patients were treated with L400/IVA for up to 24 weeks. Most patients experienced an AE during the 24-week study period with infective pulmonary exacerbations (59%), abnormal respiration (57%), cough (46%), and dyspnea (44%) reported most frequently. Eight patients (17%) stopped treatment due to AEs, including abnormal respiration (three patients), and dyspnea or dyspnea exertional (three patients), and 18 patients (39%) experienced one or more SAE. In Study 106, the frequency of SAEs, withdrawals due to AEs, and respiratory-related AEs were reported more frequently than in LUM/IVA clinical trials that enrolled patients with $ppFEV_1 > 40$.

At baseline the mean $ppFEV_1$ was 29.1 (SD: 5.1) and showed an initial decrease from baseline (at day 15), but was similar to baseline at weeks 4, 8, 16, and 24. The least squares mean change from baseline to week 24 in the $ppFEV_1$ was –0.4; 95% CI –1.9 to 1.1 based the MMRM analysis. Three patients (7%) had an absolute increase in $ppFEV_1$ of 5% or greater at week 24. Data for the respiratory domain of the CFQ-R and body mass index showed no change from baseline over 24 weeks. Of note, data were missing from 4% of patients (at day 15) to 30% of patients (at week 24) for the efficacy outcome measures.

During Study 106 the mean normalized total duration of IV antibiotics for sinopulmonary signs and symptoms was 11.4 days (SD: 18.2) and the annual all-cause hospitalization rate was 1.14, 95% CI 0.70 to 1.84. In comparison, IV antibiotic use and hospitalization rate was higher in the 24 weeks prior to the start of the trial based on data collected retrospectively. As noted in the clinical study report, these comparisons may be confounded by the differences between the data collected on study as compared with the data collected retrospectively for the 24 weeks before study enrolment.[28]

No conclusions can be made with regards to the efficacy of L400/IVA in this population given the lack of a concurrent control group, limited sample size, and the extent of missing data.

Appendix 6: Summary of PROGRESS and Registry Analysis

The objective of this appendix is to provide a summary and critical appraisal of the:

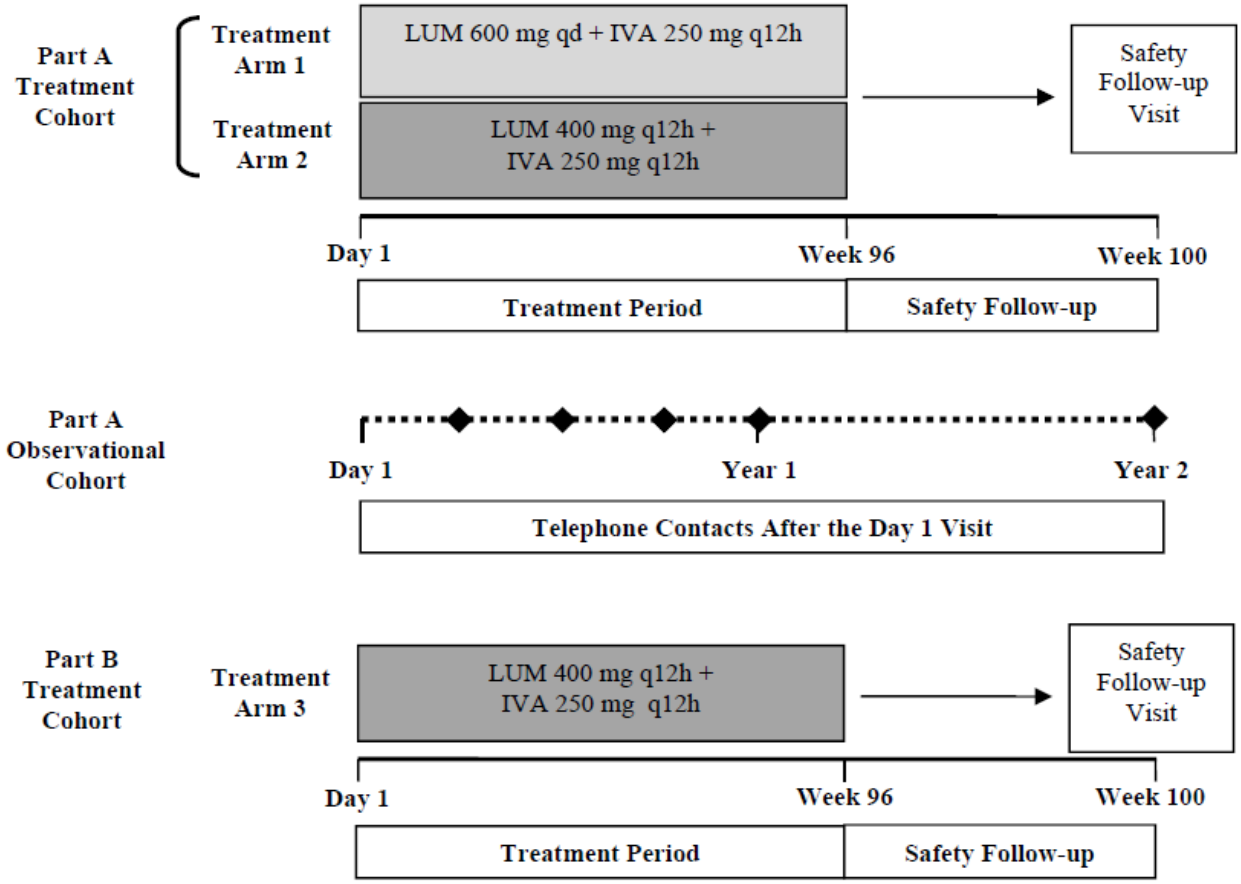
- final analysis from the PROGRESS extension study[30,31]
- manufacturers matched cohort registry analysis.[31]

PROGRESS Extension Study

Study Design

PROGRESS was a phase III, parallel-group, multicenter, rollover study that consisted of two parts (depicted in Figure 14). Part A included two treatment groups and an observational group, whereas Part B only included one treatment group. For the purpose of this summary, only Part A, treatment group 2, will be discussed. Part A, treatment group 1, was excluded from this summary as the dose of lumacaftor/ivacaftor (LUM/IVA) is not approved by Health Canada. Part A, observational group, was also excluded as the participants in this group did not receive any LUM/IVA during PROGRESS. Finally, Part B, treatment group, was excluded from this summary as it recruited participants from cohort 4 of Study 102, which were exclusively heterozygous for the F508del-cystic fibrosis transmembrane conductance regulator (CFTR) mutation.

Figure 14: Design of the PROGRESS Extension Study



IVA = ivacaftor; LUM = lumacaftor; q12h = every 12 hours; qd = once daily.

Source: Clinical study report.[30]

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

- aged 12 years and older
- confirmed diagnosis of cystic fibrosis (CF) who were homozygous for the F508del-CFTR mutation
- completed 24 weeks of study drug treatment in TRAFFIC or TRANSPORT
- 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 one in PROGRESS, were required to have the manufacturer's approval for enrolment in the Part A treatment cohort.

Patients were excluded if they had a comorbidity or laboratory abnormality that might confound the results or present a safety risk, were pregnant or nursing, not willing to meet

the contraception requirements, had a history of drug intolerance to LUM/IVA, had previous poor adherence to study drug or procedures, or were participating in another drug trial.

The Part A treatment cohort consisted of a 96-week double-blind treatment period where patients and investigators remained blinded to the treatment. Patients treated with placebo in TRAFFIC or TRANSPORT were randomized using a 1:1 ratio to one of the two treatment groups: group 1: LUM 600 mg once daily/IVA 250 mg every 12 hours (L600/IVA); or group 2: LUM 400 mg every 12 hours/IVA 250 mg every 12 hours (L400/IVA). An interactive Web response system was used to assign patients to treatment groups and randomization was stratified by age (< 18 years versus ≥ 18 years), sex (male versus female), and per cent predicted forced expiratory volume in one second ($ppFEV_1$) severity (< 70% versus ≥ 70%) collected at baseline of the patients' previous study. Patients treated with LUM/IVA in TRAFFIC and TRANSPORT remained dose-blinded and continued to receive the same dose they received during the previous studies. A double dummy design was used to maintain blinding for patients and investigators; however, the sponsor was unblinded after 24 weeks. The treatment period was followed by a four-week safety follow-up period.

Outcomes

The primary objective of the PROGRESS study was to assess long-term safety of LUM/IVA, with secondary efficacy outcomes as follows:

- absolute change from baseline in $ppFEV_1$
- relative change from baseline in $ppFEV_1$
- absolute change from baseline in body mass index (BMI)
- absolute change from baseline in BMI z score for subjects < 20 years old
- number of pulmonary exacerbations starting from the previous study
- absolute change from baseline in Cystic Fibrosis Questionnaire – Revised (CFQ-R) respiratory domain score
- absolute change from baseline body weight
- time-to-first pulmonary exacerbation, including exacerbations in the previous study
- event of having at least one pulmonary exacerbation including exacerbations in the previous study

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

Efficacy analyses were conducted based on three different study periods: previous study period (TRAFFIC and TRANSPORT, 24 weeks); current study period (PROGRESS, up to 96 weeks); and the cumulative study period, beginning from the initial dose of active drug in TRAFFIC and TRANSPORT, or PROGRESS (for those who previously received placebo), and including up to 120 weeks of treatment.

The primary efficacy analysis was based on the cumulative study period up to week 72 of PROGRESS, as after 72 weeks ≥ 30% of patients had prematurely withdrawn from the study. Sensitivity analyses were conducted using data up to week 96. Safety analyses included data for up to 120 weeks of treatment. There was no imputation for missing data. Analyses were based on the full analysis set which included patients that received any amount of study drug.

Patient Disposition

Of the 559 patients who were randomized in TRAFFIC and the 563 randomized in TRANSPORT, 549 and 559 were dosed, respectively. A total of 1,031 patients were included in Part A of PROGRESS (93% of treated patients in TRAFFIC and TRANSPORT). Of those, 523 patients were in treatment group 1 (L600/IVA) and have been excluded from this summary. Of the 516 patients who received L400/IVA, 340 (66%) were on this dose in either TRAFFIC or TRANSPORT, and 176 patients (34%) who had previously received placebo started LUM/IVA on day one of the PROGRESS study.

In the 96-week extension study, 301 patients (59%) discontinued LUM/IVA treatment early (Table 49). The most common reason reported was “other,” which the manufacturer reported was mostly related to patients transitioning to commercial product; however, no details were provided on the number of patients who stopped for this reason. The next most common reasons for stopping treatment were adverse events (AEs) (6% and 10%) and patients who refused the drugs for other reasons (10% and 7%) in the LUM/IVA and placebo then LUM/IVA groups, respectively. Overall, 90% of patients completed the safety follow-up visit.

The analyses based on the cumulative study period included a total of 369 patients who were randomized to L400/IVA at the start of TRAFFIC or TRANSPORT.

Table 49: Patient Disposition in PROGRESS

Patient Disposition n (%)	PROGRESS	
	L400/IVA	PLC Then L400/IVA
All patients	**340**	**176**
Randomized but not dosed	1	0
Full analysis set[a]	340	176
Safety analysis set[a]	340	176
Completed treatment	142 (42)	73 (42)
Discontinued treatment	198 (58)	103 (59)
Adverse event	20 (6)	18 (10)
Refused dosing (not due to AE)	34 (10)	12 (7)
Lost due to follow-up	1 (< 1)	3 (2)
Death	1 (< 1)	0
Non-compliance with study drug	3 (1)	0
Other non-compliance	3 (1)	1 (< 1)
Physician decision	0	5 (3)
Required prohibited medication	3 (1)	3 (2)
Pregnancy	2 (< 1)	3 (2)
Study terminated by sponsor	16 (5)	3 (2)
Other	115 (34)[b]	55 (31)[b]
Completed study (attended safety follow-up visit)	301 (89)	162 (92)

AE = adverse event; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; PLC then L400/IVA = placebo in TRAFFIC or TRANSPORT then lumacaftor 400 mg/ivacaftor 250 mg every 12 hours in PROGRESS.

[a] All enrolled patients who received one or more doses of the study drug in PROGRESS.

[b] The majority of patients were reported to have discontinued treatment because they transitioned from study drug to commercially available lumacaftor/ivacaftor. No details were provided.

Source: Clinical study report.[30]

Baseline Characteristics

Patient demographics and baseline characteristics are detailed in Table 50 and were similar across the previous studies and between treatment groups in the PROGRESS FAS.

Table 50: Baseline Characteristics in PROGRESS

Category	PROGRESS (FAS)	
	L400/IVA (N = 340)	PLC Then L400/IVA (N = 176)
Female, n (%)	164 (48)	86 (49)
Age (years)		
Mean (SD)	25.1 (9.3)	24.9 (10.1)
Median (range)	24.0 (12 to 57)	23.0 (12 to 64)
12 to < 18	94 (28)	47 (27)
≥ 18	246 (72)	129 (73)
Race, n (%)		
White	335 (99)	174 (99)
Black	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Region, n (%)		
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)
FEV$_1$ (L)		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Pseudomonas positive, n (%)	261 (77)	126 (72)

BMI = body mass index; FAS = full analysis set; FEV$_1$= forced expiratory volume in one second; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; PLC then L400/IVA = placebo in TRAFFIC or TRANSPORT then lumacaftor 400 mg/ivacaftor 250 mg every 12 hours in PROGRESS; Min = minimum; Max = maximum; NR = not reported; ppFEV$_1$= per cent predicted forced expiratory volume in one second; SD = standard deviation.

Note: Baseline characteristics are based on the start of TRAFFIC and TRANSPORT for all patients who received lumacaftor/ivacaftor.

Source: Clinical study report.[30]

Exposure to Study Treatment

In the PROGRESS study, the treatment exposure was similar among patients who continued on LUM/IVA and those who transitioned from placebo to active treatment in PROGRESS (median: 1.7 years) (Table 51). More than 80% of patients were treated for at least 72 weeks, with approximately a third of patients receiving treatment for the full 96-week extension study period.

Table 51: Exposure to Lumacaftor/Ivacaftor in PROGRESS

	LUM 400/IVA (N = 340)	PLC then L400/IVA (N = 176)
Total exposure in patient-years	[redacted]	[redacted]
Median exposure duration (days), (range)	[redacted]	[redacted]
Exposure duration, n (%)		
> 0 to < 24 weeks	[redacted]	[redacted]
≥ 24 to < 48 weeks	[redacted]	[redacted]
≥ 48 to < 72 weeks	[redacted]	[redacted]
≥ 72 to < 96 weeks	[redacted]	[redacted]
≥ 96 weeks	[redacted]	[redacted]

L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; PLC then L400/IVA = placebo in TRAFFIC or TRANSPORT then lumacaftor 400 mg/ivacaftor 250 mg every 12 hours in PROGRESS.

Source: Clinical study report.[30]

Efficacy

Pulmonary Exacerbations

The rate of pulmonary exacerbations was similar in the patients who received L400/IVA over the cumulative 120-week study period (events per patient-year: 0.65 [95% confidence interval (CI), 0.56 to 0.75]), and those patients who transitioned from placebo to L400/IVA at the start of the PROGRESS study (events per patient-year: 0.69 [95% CI, 0.56 to 0.85]) (Table 52). The rate of pulmonary exacerbations requiring hospitalization was 0.24 (95% CI, 0.19 to 0.29) and 0.30 (95% CI, 0.22 to 0.40) events per patient-year, and pulmonary exacerbations requiring IV antibiotics was 0.32 (95% CI, 0.26 to 0.38) and 0.37 (95% CI, 0.29 to 0.49) events per patient-year in the L400/IVA and placebo then L400/IVA groups, respectively. Time-to-first pulmonary exacerbation is shown in Figure 15.

Table 52: Pulmonary Exacerbations in PROGRESS

End Points	PROGRESS		Placebo from TRAFFIC/ TRANSPORT (24 Weeks)[c] (N = 371)
	L400/IVA (120 Weeks)[a] (N = 369)	PLC then L400/IVA (96 Weeks)[b] (N = 176)	
Pulmonary Exacerbations			
Number of patients with event, n (%)[d]	[redacted]	[redacted]	[redacted]
Number of events per patient-year (95% CI)[d]	[redacted]	[redacted]	[redacted]
Kaplan–Meier Estimate of Event-Free Survival			
Week 24	0.70 (0.65, 0.74)	0.72 (0.64 to 0.78)	0.56 (0.51 to 0.61)
Week 96	0.44 (0.38, 0.49)	0.41 (0.33 to 0.49)	NA
Week 120	0.36 (0.31 to 0.41)	NA	NA
Pulmonary Exacerbations Requiring Hospitalization			
Number of patients with event, n (%)[d]	[redacted]	[redacted]	[redacted]
Number of events per patient-year (95% CI)[d]	[redacted]	[redacted]	[redacted]
Pulmonary Exacerbations Requiring IV Antibiotics			
Number of patients with event, n (%)[e]	[redacted]	[redacted]	[redacted]
Number of events per patient-year (95% CI)[e]	[redacted]	[redacted]	[redacted]

CI = confidence interval; IV = intravenous; LUM 400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; NA = not applicable; NR = not reported; PLC then LUM 400/IVA = placebo in TRAFFIC or TRANSPORT then lumacaftor 400 mg/ivacaftor 250 mg every 12 hours in PROGRESS.

[a] Cumulative study period for TRAFFIC, TRANSPORT, and PROGRESS (up to 120 weeks of treatment).

[b] Treatment period for PROGRESS study (up to 96 weeks).

[c] Placebo results at week 24 from TRAFFIC and TRANSPORT.

[d] Note that the follow-up time varies between groups and should be considered when interpreting the percentage of patients with an event.

[e] Negative binomial regression model with covariates of previous study (TRAFFIC and TRANSPORT), treatment, sex, age (< 18, ≥ 18 years), $ppFEV_1$ at screening (< 70 or ≥ 70), and log of time spent in each study period (in patient-years) as the offset.

Source: Clinical study report.[30]

Figure 15: Time-to-first pulmonary exacerbation in PROGRESS

Confidential figure redacted at manufacturer's request.

FAS = full analysis set; L400/I = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; L600/I = lumacaftor 600 mg daily/ivacaftor 250 mg every 12 hours; P-L400/I or P-L600/I = placebo then lumacaftor/ivacaftor.

Source: Clinical study report.[30]

Forced Expiratory Volume in One Second

Figure 16 shows the absolute change and relative change from baseline $ppFEV_1$ for the cumulative study period ending at week 72 of the PROGRESS extension study. At baseline, the mean $ppFEV_1$ was 60.5% and 60.2% in the L400/IVA and the placebo then L400/IVA groups, respectively (Table 53). Both L400/IVA groups showed an initial increase in $ppFEV_1$ that ranged from 2.2% to 3.4% for the least squares (LS) mean change from baseline to 24 weeks after starting treatment. At PROGRESS week 72, the LS squares mean change from baseline in $ppFEV_1$ was 0.5% (95% CI, –0.4 to 1.5) in the patients who continued L400/IVA since TRAFFIC/TRANSPORT, and 1.5% (95% CI, 0.2 to 2.9) in patients who transitioned from placebo.

The proportion of patients with ≥ 3% or ≥ 5% increase in $ppFEV_1$ is reported in Figure 17. After the first 24 weeks of treatment 37% and 44% of patients in the L400/IVA and placebo then L400/IVA groups, respectively, had ≥ 3% increase in $ppFEV_1$, and 29% and 36% had ≥ 5% increase. The proportion of responders decreased over time, with 27% to 32% reporting a ≥ 3% and 21% to 24% showing a ≥ 5% increase at week 72 of PROGRESS.

Of note, the number of patients reporting FEV_1 data decreased over time (Table 53), and data were missing for 25% of patients by PROGRESS week 72, and for 59% of patients by week 96.

Table 53: Absolute Change in $ppFEV_1$ in PROGRESS

End Points	PROGRESS				PLC from TRAFFIC/ TRANSPORT (24 weeks)[c] (N = 371)	
	L400/IVA (120 weeks)[a] (N = 369)		PLC then L400/IVA (96 weeks)[b] (N = 176)			
	N (%)[d]	Parameter	N (%)[d]	Parameter	N (%)[d]	Parameter
Baseline, mean (SD)	365 (99)	60.5 (14.1)	175 (99)	60.2 (14.7)	366 (99)	60.4 (13.8)
TRAFFIC/TRANSPORT LSM change (95% CI)	339 (92)	2.2 (1.4 to 2.9)	NA		349 (94)	–0.4 (–1.1 to 0.4)
PROGRESS week 24 LSM change (95% CI)	295 (80)	2.7 (1.8 to 3.6)	154 (88)	3.4 (2.2 to 4.7)	NA	
PROGRESS week 48 LSM change (95% CI)	282 (76)	1.4 (0.5 to 2.4)	140 (80)	2.1 (0.8 to 3.4)		
PROGRESS week 72 LSM change (95% CI)	273 (74)	0.5 (–0.4 to 1.5)	134 (76)	1.5 (0.2 to 2.9)		
PROGRESS week 96 LSM change (95% CI)	147 (40)	0.5 (–0.7 to 1.6)	75 (43)	0.8 (–0.8 to 2.3)		

CI = confidence interval; LSM = least squares mean; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; NA = not applicable; PLC then L400/IVA = placebo in TRAFFIC or TRANSPORT then lumacaftor 400 mg/ivacaftor 250 mg every 12 hours in PROGRESS; $ppFEV_1$= per cent predicted forced expiratory volume in one second; SD = standard deviation.

[a] Cumulative study period for TRAFFIC, TRANSPORT, and PROGRESS (up to 120 weeks of treatment).

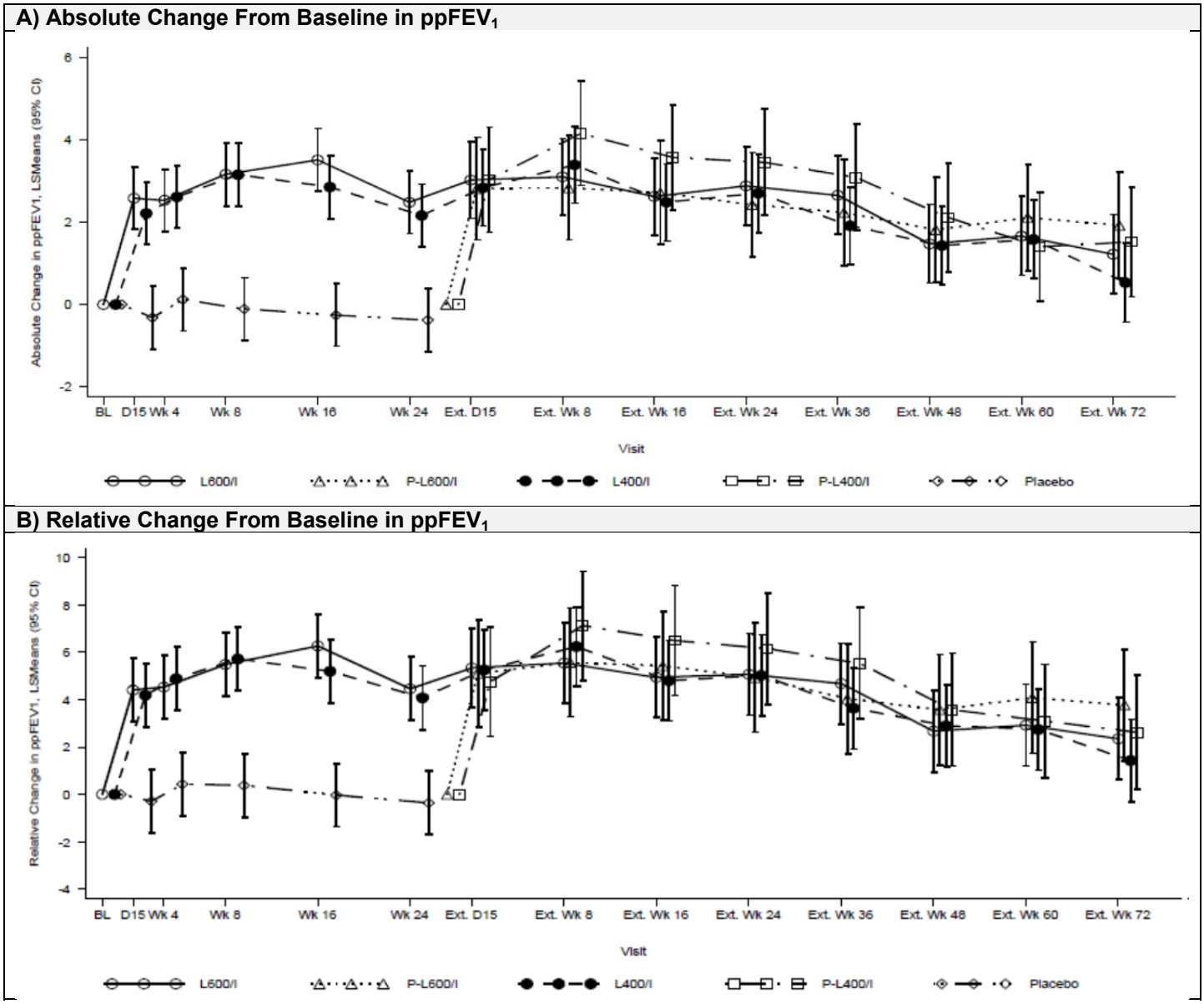
[b] Treatment period for PROGRESS study (up to 96 weeks).

[c] Placebo results at week 24 from TRAFFIC and TRANSPORT.

[d] Number of patients with data at the time point and the percentage of the total number of patients included in the analysis.

Source: Clinical study report.[30]

Figure 16: Absolute and Relative Change From Baseline in $ppFEV_1$ in PROGRESS

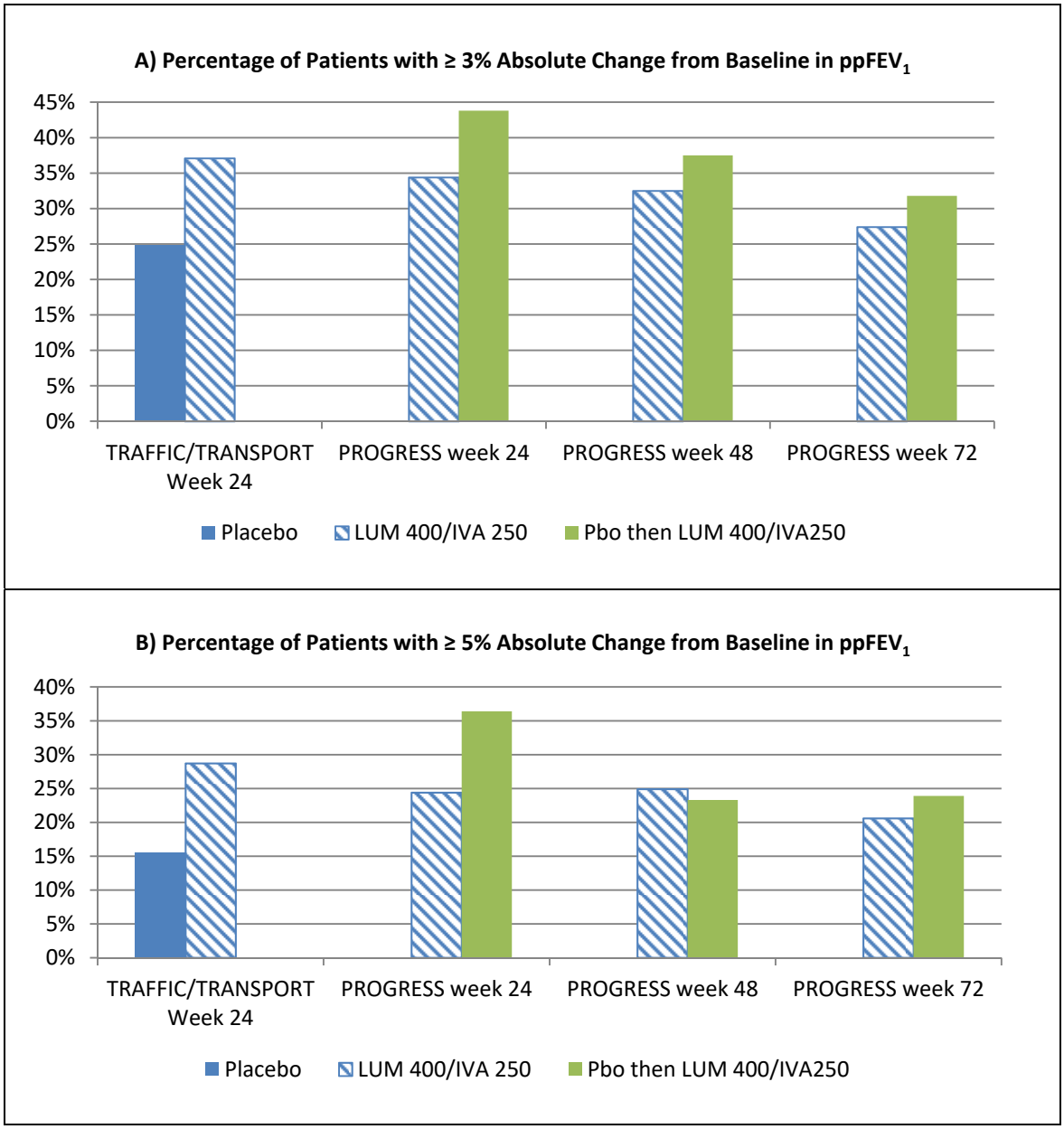


BL = baseline; CI = confidence interval; D = day; Ext. = extension phase; LS = least squares; L400/I = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; L600/I = lumacaftor 600 mg daily/ivacaftor 250 mg every 12 hours; MMRM = mixed-effects model for repeated measures; P-L400/I or P-L600/I = placebo then lumacaftor/ivacaftor; $ppFEV_1$= per cent predicted forced expiratory volume in one second; Wk = week.

Note: MMRM with patient as random effect, and treatment, visit, treatment-visit interaction as fixed effect, with adjustment for sex, previous study (TRAFFIC versus TRANSPORT), age (< 18 versus ≥ 18 years), $ppFEV_1$ at screening (< 70 versus ≥ 70). Separate models were run for the previous study period (TRAFFIC and TRANSPORT) and current study period (PROGRESS). Analysis includes all measurements up to week 72 of Study 105, both on-treatment measurements and measurements after treatment discontinuation.

Source: Clinical study report.[30]

Figure 17: Responder Analysis for $ppFEV_1$ in PROGRESS



L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; PLC = placebo; $ppFEV_1$ = per cent predicted forced expiry volume in one second.

Source: Prepared by CADTH using data from the clinical study report.[30]

Body Mass Index

Data on the absolute change from baseline in BMI and BMI z score are presented in Table 55. Outcome data were missing for 18% to 35% of patients at PROGRESS week 72. The mean BMI showed an increase over time from baseline values of 21.5 kg/m^2 and 20.9 kg/m^2 per group, and a LS mean change from baseline of 0.69 to 0.62 kg/m^2 at PROGRESS week 72 for the L400/IVA and placebo then L400/IVA groups, respectively (Figure 18). The BMI z score was calculated for the subgroup of patients < 20 years of age (34%). The mean BMI z scores ranged from –0.35 to –0.63 at baseline and showed an increase with treatment, although by PROGRESS week 72, the BMI z scores were similar to baseline. At all time points the CIs were wide (Figure 18).

Table 54: Absolute Change in BMI and BMI Z Score in PROGRESS

End points	PROGRESS			
	L400/IVA (120 weeks)[a] (N = 369)		PLC then L400/IVA (96 weeks)[b] (N = 176)	
	N (%)	Parameter	N (%)	Parameter
BMI, kg/m^2				
Baseline, mean (SD)	369 (100)	21.5 (3.0)	176 (100)	20.9 (2.8)
TRAFFIC/TRANSPORT LSM change (95% CI)	356 (96)	0.39 (0.32 to 0.46)	NA	NA
PROGRESS week 24 LSM change (95% CI)	319 (86)	0.62 (0.50 to 0.74)	165 (94)	0.41 (0.24 to 0.57)
PROGRESS week 72 LSM change from baseline to (95% CI)	289 (78)	0.69 (0.56 to 0.81)	145 (82)	0.62 (0.45 to 0.79)
BMI z score for patients < 20 years				
Baseline, mean (SD)	123 (33)	–0.35 (0.86)	65 (37)	–0.63 (0.73)
TRAFFIC/TRANSPORT LSM change (95% CI)	116 (31)	0.12 (0.06 to 0.17)	NA	NA
PROGRESS week 24 LSM change (95% CI)	100 (27)	0.17 (0.09 to 0.26)	56 (32)	0.10 (0.00 to 0.21)
PROGRESS week 72 LSM change from baseline (95% CI)	89 (24)	0.04 (-0.05 to 0.12)	42 (24)	0.08 (-0.04 to 0.19)

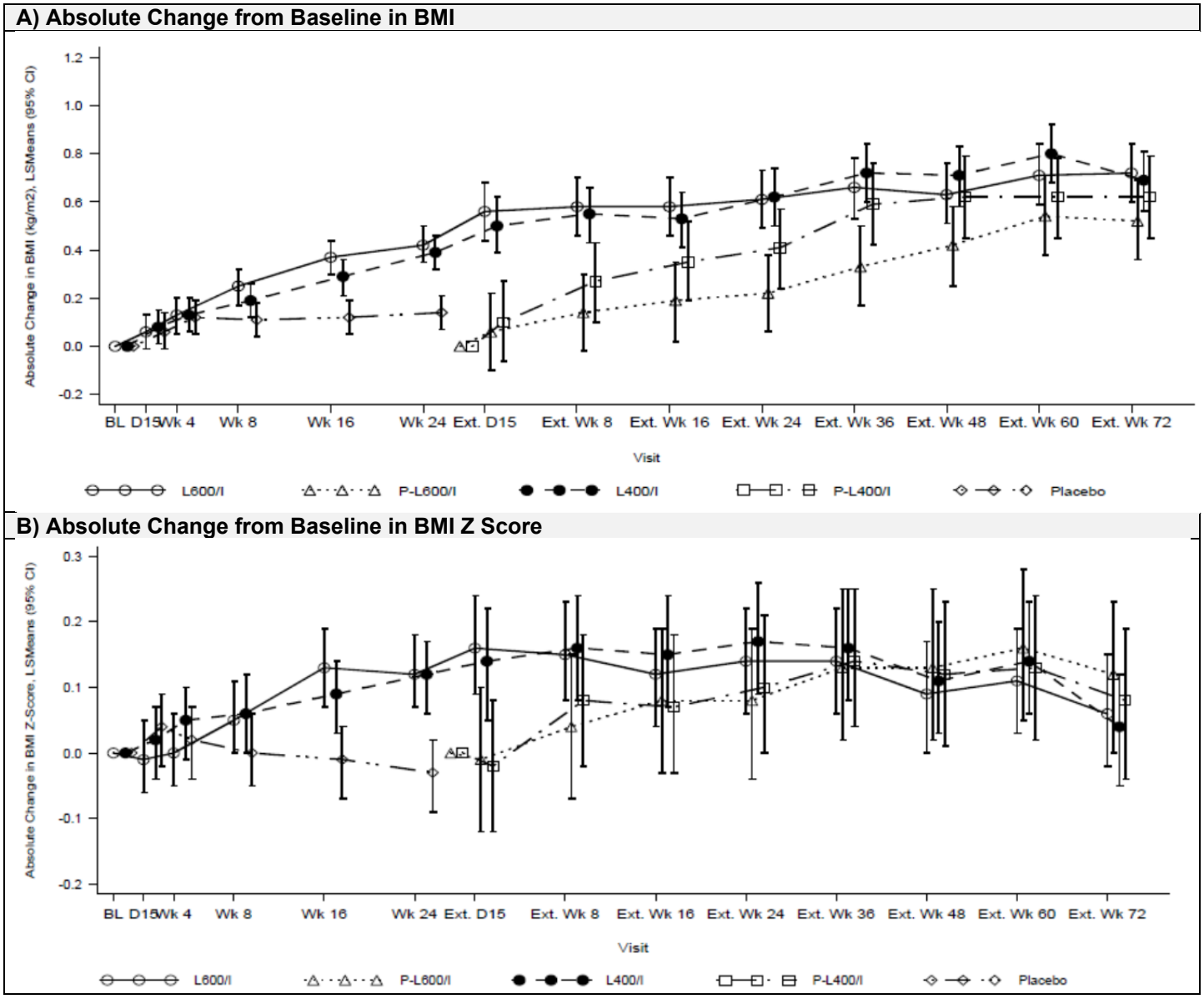
BMI = body mass index; CI = confidence interval; IV = intravenous; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; LSM = least squares mean; NA = not applicable; NR = not reported; PLC then L400/IVA = placebo in TRAFFIC or TRANSPORT then lumacaftor 400 mg/ivacaftor 250 mg every 12 hours in PROGRESS; SD = standard deviation.

[a] Cumulative study period for TRAFFIC, TRANSPORT, and PROGRESS (up to 120 weeks of treatment).

[b] Treatment period for PROGRESS study (up to 96 weeks).

Source: Clinical study report.[30]

Figure 18: Absolute Change from Baseline in BMI (A) and BMI Z Score (B) from PROGRESS



BL = baseline; BMI = body mass index; CI = confidence interval; D = day; Ext. = extension phase; LS = least squares; L400/I = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; L600/I = lumacaftor 600 mg daily/ivacaftor 250 mg every 12 hours; P-L400/I or P-L600/I = placebo then lumacaftor/ivacaftor; Wk = week.

Note: Mixed-effects model for repeated measures with patient as random effect, and treatment, visit, treatment-visit interaction as fixed effect, with adjustment for sex, previous study (TRAFFIC versus TRANSPORT), age (< 18 versus ≥ 18 years), per cent predicted forced expiratory volume in one second at screening (< 70 versus ≥ 70), and BMI at baseline. Separate models were run for the previous study period (TRAFFIC and TRANSPORT) and current study period (PROGRESS). Analysis includes all measurements up to week 72 of PROGRESS, both on-treatment measurements and measurements after treatment discontinuation.

Source: Clinical study report.[30]

Cystic Fibrosis Questionnaire – Revised

The mean respiratory domain score for the Cystic Fibrosis Questionnaire – Revised was 68.3 to 70.4 points at baseline, and generally showed an increase versus baseline with L400/IVA, although fluctuations were noted. At PROGRESS week 72, the LS mean change from baseline was 5.7 and 3.3 points for the L400/IVA and placebo then L400/IVA groups, respectively (Figure 19).Of note, data were missing for 26% of patients at extension week 72.

Table 55: Absolute Change in CFQ-R Respiratory Domain Score From PROGRESS

End Points	PROGRESS			
	L400/IVA (120 Weeks)[a] (N = 369)		PLC then L400/IVA (96 Weeks)[b] (N = 176)	
	N (%)	Parameter	N (%)	Parameter
Baseline, mean (SD)	366 (99)	68.3 (18.0)	176 (100)	70.4 (18.5)
Absolute LS mean change from baseline to extension week 72 (95% CI LS mean)	269 (73)	5.7 (3.8, 7.8)	135 (77)	3.3 (0.7, 5.9)

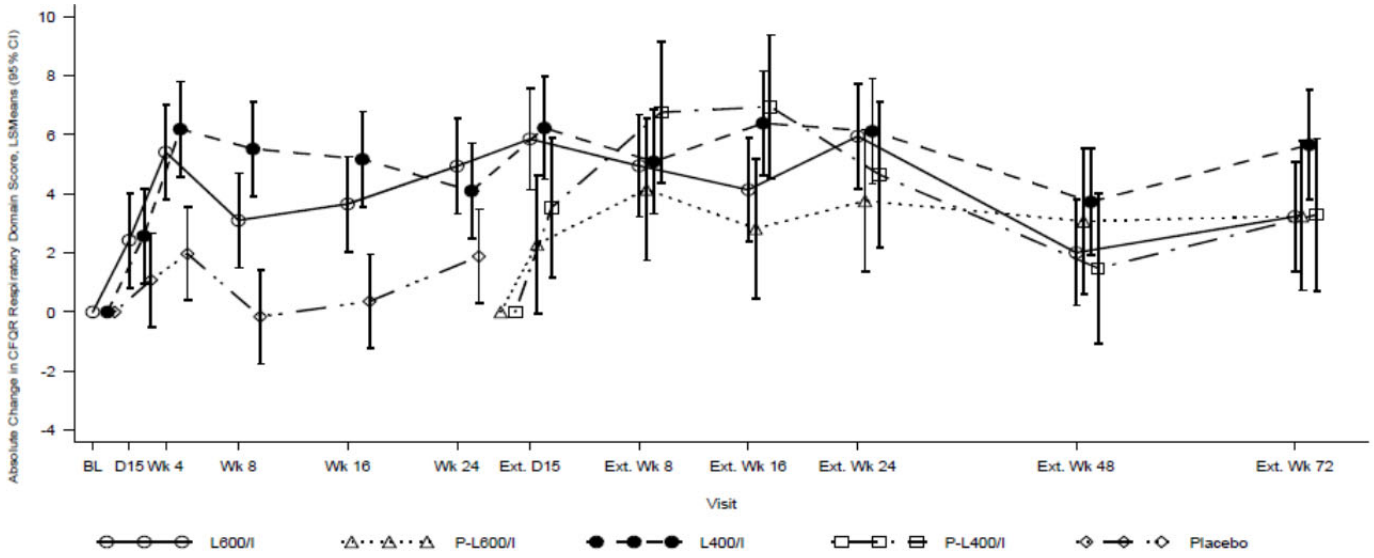
CFQ-R = Cystic Fibrosis Questionnaire – Revised; CI = confidence interval; IV = intravenous; LUM 400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; NA = not applicable; NR = not reported; PLC then L400/IVA = placebo in TRAFFIC or TRANSPORT then lumacaftor 400 mg/ivacaftor 250 mg every 12 hours in PROGRESS; LS = least squares; SD = standard deviation.

[a] Cumulative study period for TRAFFIC, TRANSPORT, and PROGRESS (up to 120 weeks of treatment).

[b] Treatment period for PROGRESS study (up to 96 weeks).

Source: Clinical study report.[30]

Figure 19: Absolute Change From Baseline in CFQ-R Respiratory Domain Score in PROGRESS



BL = baseline; CI = confidence interval; CFQ-R = Cystic Fibrosis Questionnaire – Revised; D = day; Ext. = extension phase; FAS = full analysis set; LS = least squares; L400/I = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; L600/I = lumacaftor 600 mg daily/ivacaftor 250 mg every 12 hours; MMRM = mixed-effects model for repeated measures; P-L400/I or P-L600/I = placebo then lumacaftor/ivacaftor; $ppFEV_1$= per cent predicted forced expiratory volume in one second; Wk = week.

Note: MMRM with patient as random effect, and treatment, visit, treatment-visit interaction as fixed effect, with adjustment for sex, previous study (TRAFFIC versus TRANSPORT), age (< 18 versus ≥ 18 years), $ppFEV_1$ at screening (< 70 versus ≥70), and CFQ-R respiratory domain score at baseline. Separate models were run for the previous study period (TRAFFIC and TRANSPORT) and current study period (PROGRESS). Analysis includes all measurements up to week 72 of Study 105, both on-treatment measurements and measurements after treatment discontinuation.

Source: Clinical study report.[30]

Adverse Events

Nearly all patients (99%) experienced an AE during treatment, with half of the patients reporting a serious adverse event (SAE) (Table 56). Infective pulmonary exacerbations were the most commonly reported AE (66%), which were SAEs for 35% of patients (Table 57).Other commonly reported AEs included cough (51%), increased sputum (28%), hemoptysis (25%), dyspnea (22%), and headache (22%). Ten per cent of patients stopped treatment due to AEs over the cumulative study period (up to 120 weeks).

Two deaths were reported among patients who received L400/IVA in the extension study. One 24-year-old patient had a life-threatening infective pulmonary exacerbation on day 344, developed respiratory failure on day 366, and died a few days later. A 25-year-old patient developed life-threatening distal intestinal obstructive syndrome and died on day 633.

Respiratory-related AEs of interest were reported in 40% of patients over the cumulative study period (Table 56). The frequency of these events was higher in the placebo group patients who started LUM/IVA in PROGRESS (38%) than the patients who continued on LUM/IVA during PROGRESS (29%). Two per cent of patients had a respiratory-related event that let to treatment discontinuation, and 1% had a serious respiratory AE. Elevated transaminases were reported by 9% of patients overall, with < 1% stopping treatment or reporting a serious transaminase-related AE. One patient who transitioned from placebo to LUM/IVA developed a subcapsular cataract.

Table 56: Summary of Adverse Events in PROGRESS

Summary of Adverse Events, n (%)	PROGRESS Study (96 Weeks)		Cumulative Study Period (120 Weeks)
	L400/IVA (N = 340)	PLC Then L400/IVA (N = 176)	L400/IVA (N = 545)
Any adverse events	333 (98)	176 (100)	541 (99)
WDAEs	[redacted]	[redacted]	[redacted]
SAEs	143 (42)	89 (51)	265 (49)
Deaths	[redacted]	[redacted]	[redacted]
Notable harms			
Elevated transaminases	18 (5)	17 (10)	51 (9)
Increased alanine aminotransferase	15 (4)	16 (9)	38 (7)
Increased aspartate aminotransferase	16 (5)	14 (8)	39 (7)
Increased hepatic enzyme	1 (< 1)	1 (0.6)	6 (1)
Increased transaminases	1 (< 1)	0	3 (0.6)
Transaminase-related adverse events leading to discontinuation	0	3 (1.7)	3 (0.6)
Serious transaminase-related adverse events	1 (0.3)	2 (1.1)	4 (0.7)
Respiratory-related adverse events[a]	99 (29)	67 (38)	220 (40)
Chest discomfort	4 (1)	7 (4)	16 (3)
Dyspnea	53 (16)	36 (21)	117 (22)
Abnormal respiration	[redacted]	[redacted]	[redacted]
Asthma	16 (5)	5 (3)	28 (5)
Bronchial hyperreactivity	3 (1)	0	5 (1)
Bronchospasm	8 (2)	8 (5)	20 (4)
Wheezing	13 (4)	12 (7)	35 (6)
Respiratory-related[a] adverse events leading to discontinuation	5 (1.5)	7 (4.0)	12 (2.2)
Serious respiratory-related adverse events	2 (0.6)	3 (1.7)	5 (0.9)
Cataract subcapsular	0	1 (0.6)	1 (0.2)

L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; PLC then L400/IVA = placebo in TRAFFIC or TRANSPORT then lumacaftor 400 mg/ivacaftor 250 mg every 12 hours in PROGRESS; SAE = serious adverse event; WDAE = withdrawals due to adverse event.

[a] Specific adverse events included asthma, bronchial hyperreactivity, bronchospasm, chest discomfort, dyspnea, abnormal respiration, and wheezing.

Source: Clinical study report.[30]

Table 57 : Summary of Adverse Events Cumulative to Week 120 in PROGRESS

Summary of Adverse Events	L400/IVA (N = 545)
Most Common Adverse Events (≥ 10%)	
Any adverse events, n (%)	541 (99)
Infective pulmonary exacerbation of CF	359 (66)
Cough	276 (51)
Increased sputum	152 (28)
Hemoptysis	135 (25)
Headache	121 (22)
Dyspnea	117 (22)
Pyrexia	103 (19)
Nasopharyngitis	114 (21)
Diarrhea	105 (19)
Nausea	100 (18)
Abnormal respiration	88 (16)
Upper respiratory tract infection	104 (19)
Oropharyngeal pain	85 (16)
Fatigue	85 (16)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Serious Adverse Events	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Treatment Discontinuation Due to Adverse Events	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CF = cystic fibrosis; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; SAE = serious adverse events; WDAE = withdrawals due to adverse events.

Data are cumulative and include adverse events from TRAFFIC and TRANSPORT as well as PROGRESS. Specific adverse events occurring in at least 1% of patients were listed.

Source: Clinical study report.[30]

Registry Comparator Analysis

Study Design

Konstan et al.[31] conducted a post hoc rate of change analysis that compared patients who received L400/IVA in PROGRESS to patients in the US Cystic Fibrosis Foundation Patient Registry (CFFPR). To be eligible for this analysis, patients enrolled in PROGRESS must have had three or more non-missing $ppFEV_1$ measurements over at least 0.5 years after having received treatment for > 21 days, and were matched to at least one patient from the US CFFPR. Patients were matched with up to five registry controls who were at least 12 years of age in 2012, with a confirmed diagnosis of CF (in 2012 or earlier), and were homozygous for F508del CFTR.[31] Other inclusion criteria were: no evidence of transplant or death from birth through the end of 2012; no evidence of pregnancy in 2012; valid entries for sex, race and birth year; and had nutritional and spirometry data from at least one stable encounter in 2012 (defined as an encounter with no material change in lung function or routine medication from the prior encounter and no evidence of a care episode).[31] The baseline visit for each patient was randomly selected from stable encounters during 2012.[31] Eligible control patients had to have ≥ 3 non-missing FEV_1 records spanning ≥ 0.5 years after baseline and prior to death, transplant, or pregnancy, or two years post-baseline, whichever occurred earlier.[31]

A propensity score approach was used for matching PROGRESS patients with those from the US registry. Propensity scores were generated using a logistic regression model that included variables associated with lung function decline (Table 58).[95,119,120] Excluded from the model were Haemophilus influenza, non-tuberculosis mycobacterium, BMI z score, oral corticosteroids, and inhaled corticosteroids, as these variables did not meet the statistical significance threshold of < 0.2.[31]

Each control patient was assessed as a match to each LUM/IVA-treated patient if the absolute difference for the logit of the propensity score was ≤ 0.2. Matching was stratified by $ppFEV_1$ (< 40, 40 to 70, > 70) and age (< 18 years, ≥ 18 years).[31] An iterative approach was used to select matches, as described by Millar and Pasta.[121] First, the matching algorithm searched for all acceptable matches possible, based on the patients' propensity score and stratification variable. Using the number of acceptable matches as the criterion, the hardest-to-match treated patient was matched with the hardest-to-match control. The matched control patient was removed from the pool of potential matches and the matching process was repeated until a maximum of five matches were obtained for a given treated patient. The algorithm iterated until all possible matches were identified.[121]

Table 58: Risk Factors Included in Propensity Score Logistic Regression Model

Binary	Continuous
• Sex • Race • CF-related diabetes • Baseline tests for *Burkholderia* species, *Aspergillus*, *Alcaligenes*, *Stenotrophomonas*, *Pseudomonas aeruginosa* cultures, methicillin-resistant *Staphylococcus aureus*, and methicillin-sensitive *Staphylococcus aureus* • Baseline usage of acetylcysteine, inhaled aztreonam, colistin, dornase alfa, leukotriene modifiers, and tobramycin	• Baseline age • Height-for-age z score • Weight-for-age z score • BMI • $ppFEV_1$ (based on Global Lungs Function Initiative equations) • Per cent predicted forced vital capacity • Per cent predicted FEV_1/FVC ratio • Per cent predicted forced expiratory flow (mid-expiratory range) • Decile for baseline $ppFEV_1$

BMI = body mass index; CF = cystic fibrosis; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; $ppFEV_1$ = per cent predicted forced expiratory volume in one second.

Source: Konstan et al.[31]

Outcomes

The primary outcome was the rate of change in $ppFEV_1$ for LUM/IVA versus matched-registry controls. Other outcomes included the rate of change in weight-for-age z scores, BMI z scores, and BMI. Weight-for-age z scores were based on the Center for Disease Control growth chart with adults > 20 years of age treated as if they were 20 years of age.[31] Differences in rate of change were analyzed using a mixed model, with intercepts and slopes for each match group and patient-within-match group (generally one LUM/IVA patient and up to five controls) as random effects and unstructured covariances.[31] Fixed effects for LUM/IVA or control and age (< 18 or ≥ 18 years of age) were included to test intercept and slope differences across patients and within age group.[31] Baseline measures were not included in the model (i.e., only post-baseline outcome data were included) and all analyses excluded outcome data for the first 21 days of treatment for clinical trial patients. Data from the PROGRESS study up to week 96 were included; thus, patients who were transitioned from placebo to LUM/IVA had a maximum of 96 weeks of treatment, and those initiated on LUM/IVA in TRAFFIC or TRANSPORT had a maximum treatment duration of 120 weeks.[31] Registry data were included for up to two years post baseline and patients in both the LUM/IVA and control groups were censored upon loss to follow-up.[31]

The annualized mean rate of change in FEV_1 was estimated using all available FEV_1 measures (Global Lung Function Initiative equation), except for those in the first 21 days after baseline for the LUM/IVA group. The authors stated this exclusion omitted any data related to the initial increase in FEV_1 observed with treatment initiation. Sensitivity analyses were conducted that used the Wang-Hankinson equation to calculate $ppFEV_1$, and that adjusted for baseline variables that differed between PROGRESS patients and matched controls. Differences in baseline characteristics were those with $P < 0.10$ from demographic and baseline characteristics subsets (< 18 years of age and ≥ 18 years of age) including age, height-for-age z score, $ppFEV_1$, $ppFEV_1$ decile, forced vital capacity (FVC) per cent predicted, FEV_1/FVC per cent predicted, FEF25-75 per cent predicted, dornase alfa, tobramycin, aztreonam, leukotriene modifiers, *Aspergillus*, *Alcaligenes*, *Burkholderia* species, methicillin-resistant *Staphylococcus aureus* (MRSA), and methicillin-sensitive *Staphylococcus aureus* (MSSA).[31]

Propensity Score Matching

Out of 4,869 registry patients who met the inclusion criteria, 4,664 met the follow-up data requirements (≥ 3 FEV_1 measures over ≥ 0.5 years before death, transplant or pregnancy; or two years post baseline, whichever occurred earlier). Of these, 1,588 control patients were matched to 455 patients who received L400/IVAin the PROGRESS study. No match was found for 24 patients (5%) in the PROGRESS study, and another 37 PROGRESS patients (7%) were excluded from the analysis as they did not meet the requirement for post-baseline FEV_1 measurements or follow-up. The proportion of patients from PROGRESS that were matched to one to five registry patients was as follows: (1:1) 18%; (1:2) 16%; (1:3) 11%; (1:4) 8%; (1:5) 47%.

Baseline characteristics were generally similar between the LUM/IVA patients included in the registry comparator analysis and matched controls from the US CFFPR, although the data reported was limited (Table 50). Balance diagnostics, in the form of effect size for baseline covariates included in the propensity score logistic regression model, were also reported (Table 59 and Table 60). These data showed a number of potential confounders that may not have been distributed equally between the treatment and control groups. Specifically, $ppFEV_1$ and ppFVC showed a mean difference of 1.91 and 1.96 between groups, respectively (effect size -0.12 and -0.13 for LUM/IVA minus CFFPR). In addition, more patients in the control group had MRSA or MSSA (effect size –0.14 and –0.12), and more were receiving treatment with dornase alfa, aztreonam, or tobramycin (effect size –0.12 to –0.15), compared with the LUM/IVA group. The manufacturer considered an effect size of < 0.2 to be a small and therefore acceptable difference between groups.[122]Typically, standardized differences of < 0.1 have been taken to indicate a negligible difference in the mean or prevalence of a covariate between groups, although the threshold used may vary.[123,124] No other balance diagnostics data, such as box plots or cumulative distribution plots,[123,124] were presented as evidence to demonstrate that the propensity score model was adequately specified. As a result, it is unclear if balance was achieved across the entire range of propensity scores and within important subgroups of patients.

Table 59: Effect Sizes for Binary Variables Used for Propensity Score Matching — Registry Comparator Analysis

	Proportion of LUM/IVA patients with attribute	Proportion of control patients with attribute	Standard deviation	Effect size
Female	0·47	0·47	0·50	0·01
White	0·98	0·98	0·13	0·04
CF-related diabetes	0·29	0·32	0·46	-0·07
Nontuberculosis mycobacterium	0·06	0·04	0·22	0·08
Aspergillus	0·41	0·38	0·49	0·06
Burkholderia species	0·02	0·04	0·17	-0·07
Haemophilus influenzae	0·15	0·16	0·36	-0·01
MRSA	0·22	0·28	0·43	-0·14
MSSA	0·40	0·46	0·49	-0·12
Pseudomonas aeruginosa	0·75	0·74	0·43	0·03
Alcaligenes	0·08	0·10	0·29	-0·06
Stenotrophomonas	0·18	0·21	0·40	-0·09
Tobramycin	0·31	0·37	0·47	-0·15
Colistin	0·07	0·07	0·26	0·00
Aztreonam	0·20	0·25	0·41	-0·12
Dornase alfa	0·75	0·80	0·42	-0·14
Acetylcysteine/Mucomyst	0·01	0·01	0·09	0·00
Corticosteroids, oral	0·05	0·05	0·21	0·02
Corticosteroids, inhaled	0·17	0·18	0·38	-0·03
Leukotriene modifiers	0·15	0·17	0·37	-0·07

CF = cystic fibrosis; LUM/IVA = lumacaftor/ivacaftor; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*.

Source: Reprinted from The Lancet Respiratory Medicine, 5(2), Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, et al., Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase III, extension study, 107-118, Copyright (2017), with permission from Elsevier.[31]

Table 60: Effect Sizes for Binary Variables Used for Propensity Score Matching — Registry Comparator Analysis

	Mean difference between groups (LUM/IVA minus control)	Pooled standard deviation for difference	Effect size
Age	-0·58	9·34	0·06
Height-for-age *z* score	-0·10	1·01	0·09
Weight-for-age *z* score	-0·05	0·95	0·05
BMI	0·03	3·08	-0·01
BMI *z* score	0·01	0·92	-0·01
$ppFEV_1$	1·91	15·80	-0·12
ppFVC	1·96	15·29	-0·13
$ppFEV_1$/ppFVC ratio	0·48	11·49	-0·04
$ppFEF_{25-75}$	1·79	19·34	-0·09
Decile for $ppFEV_1$	0·11	2·02	-0·05

BMI = body mass index; LUM/IVA = lumacaftor/ivacaftor; $ppFEF_{25-75}$ = per cent predicted forced expiratory flow 25% to 75%; $ppFEV_1$= per cent predicted forced expiratory volume in one second; ppFVC = per cent predicted forced vital capacity.

Source: Reprinted from The Lancet Respiratory Medicine, 5(2), Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, et al., Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase III, extension study, 107-118, Copyright (2017), with permission from Elsevier.[31]

Baseline Characteristics

Patient demographics and baseline characteristics are detailed in Table 61 (see data from rate of change analysis). The mean age was 25 years, and approximately half of the patients were female. The mean $ppFEV_1$ at baseline was 59.8 in the LUM/IVA group and 61.8 in the registry control group. The proportion of patients with $ppFEV_1$ < 40, 40 to < 70, and ≥ 70 at baseline was 9%, 65%, and 26% in the LUM/IVA-treated patients and 9%, 59%, and 32% in the US registry patients, respectively.[122]

The time to last post-baseline visit was 1.86 years (standard deviation [SD]: 0.40; range 0.6 to 2.43) in the LUM/IVA group and 1.85 (SD: 0.21; range 0.53 to 2.00) in the registry group.[122]

Table 61: Baseline Characteristics in Registry Comparator Analysis

	PROGRESS		Rate of change analysis	
	Placebo transitioned to lumacaftor 400 mg every 12 h/ivacaftor 250 every 12 h* (n=176)	Lumacaftor 400 mg every 12 h/ivacaftor 250 every 12 h* (n=340)	CFFPR matched-controls† (n=1588)	Lumacaftor 400 mg every 12 h/ivacaftor 250 every 12 h‡ (n=455)
Women	86 (49%)	164 (48%)	745 (47%)	216 (47%)
Age (years)	24·9 (10·1)	25·1 (9·3)	25·2 (9·3)	25·8 (9·6)
Age groups (years)				
12–<18	47 (27%)	94 (28%)	396 (25%)	117 (26%)
≥18	129 (73%)	246 (72%)	1192 (75%)	338 (74%)
$ppFEV_1$§	60·2 (13·8)	60·4 (14·2)	61·8 (16·3)	59·8 (13·8)
Body-mass index (kg/m²)	20·9 (2·8)	21·4 (2·9)	21·3 (3·1)	21·3 (2·9)
Pseudomonas positive	126 (72%)	261 (77%)	1178 (74%)	343 (75%)

Data are n (%) or mean (SD). CFFPR=Cystic Fibrosis Foundation Patient Registry. $ppFEV_1$=percent predicted FEV_1. *Data reported are baseline from TRAFFIC or TRANSPORT for patients who rolled over into PROGRESS. †Baseline was the later of two stable visits in 2012 (ie, no evidence of a care episode and no material change in $ppFEV_1$ or change in any routine drug treatment). ‡Baseline visit was the day of lumacaftor/ivacaftor start. §Wang-Hankinson equations were used to calculate $ppFEV_1$ in PROGRESS; Global Lungs Initiative equations were used to calculate $ppFEV_1$ in the rate of change analysis.

***Table 1:* Patient demographics and baseline characteristics for patients who rolled over into PROGRESS and for patients included in the rate of change analysis**

CFFPR = Cystic Fibrosis Foundation Patient Registry; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; SD = standard deviation.

Source: Reprinted from The Lancet Respiratory Medicine, 5(2), Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, et al., Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase III, extension study, 107-118, Copyright (2017), with permission from Elsevier.[31]

Efficacy

The results of the annual rate of change analysis is presented in Table 62 and Table 63, and graphically presented in Figure 20 and Figure 21.

Table 62: Summary of Results from Registry Comparator Analysis

Outcome	L400/IVA (N = 455)	US CFFPR matched control (N = 1,588)	*P* value
Annualized rate of change in $ppFEV_1$ (95% CI)[a]	–1.33 (–1.80 to –0.85)	–2.29 (–2.56 to –2.03)	< 0.001
Annualized rate of change in weight-for-age z score (95% CI)[a]	0.033 (0.006 to 0.061)	–0.030 (–0.045 to –0.015)	< 0.001
Annualized rate of change in BMI z score (95% CI)[a]	0.028 (–0.004 to 0.050)	–0.040 (–0.057 to –0.023)	< 0.001
Annualized rate of change in BMI (kg/m^2) (95% CI)[a]	0.259 (0.170 to 0.349)	0.100 (0.051 to 0.149)	0.002

BMI = body mass index; CFFPR = Cystic Fibrosis Foundation Patient Registry; CI = confidence interval; L400/IVA = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours; $ppFEV_1$ = per cent predicted forced expiratory volume in one second.

[a] Includes data through to extension week 96 for the L400/IVA group.

Source: Konstan et al.[31]

Table 63: Sensitivity Analyses for Annualized Rate of Change in $ppFEV_1$ from Registry Comparator Analysis

	LUM 400 mg q12h/IVA 250 mg q12h (n=455)	Control (n=1588)	Relative reduction	p Value
Analysis through extension week 72	-1·39 (-1·92, -0·86)	-2·29 (-2·56, -2·02)	39%	0·003
Wang-Hankinson equations	-1·54 (-2·02, -1·05)	-2·56 (-2·83, -2·29)	40%	<0·001
Adjustment for baseline variables [a]	-1·29 (-1·76, -0·82)	-2·30 (-2·56, -2·04)	44%	<0·001

LUM = lumacaftor; IVA = ivacaftor; $ppFEV_1$ = per cent predicted forces expiry volume in one second; q12h = every 12 hours.

Note: Estimated annualized rate of change in $ppFEV_1$ (95% CI) through extension week 96 (unless otherwise indicated).

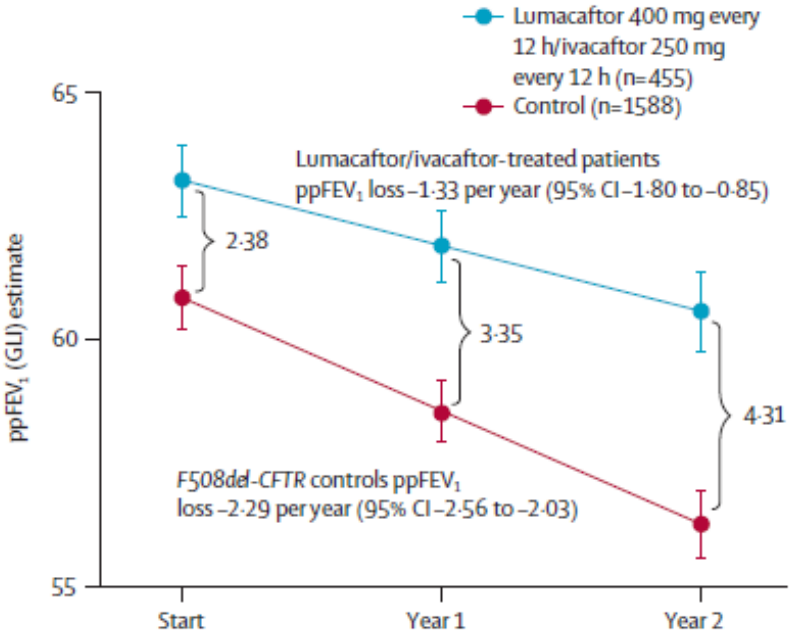
[a] Variables included age, height-for-age z score, $ppFEV_1$, $ppFEV_1$ decile, FVC per cent predicted, FEV_1/FVC per cent predicted, FEF25-75 per cent predicted, dornase alfa, tobramycin, aztreonam, leukotriene modifiers, *Aspergillus*, *Alcaligenes*, *Burkholderia* species, methicillin-resistant *Staphylococcus aureus*, and methicillin-sensitive *Staphylococcus aureus*.

Source: Reprinted from The Lancet Respiratory Medicine, 5(2), Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, et al., Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase III, extension study, 107-118, Copyright (2017), with permission from Elsevier.[31]

Forced Expiratory Volume in One Second

Among patients who received L400/IVA, the annualized rate of change in the $ppFEV_1$ was –1.33% (95% CI, –1.80 to –0.85), compared with –2.29% (95% CI, –2.56 to –2.03) in the registry control group. Similar results were reported for the sensitivity analyses that truncated data for the L400/IVA group at extension week 72, calculated $ppFEV_1$ based on the Wang-Hankinson equation, and adjusted for 16 baseline characteristics that differed between L400/IVA and control groups ($P < 0.10$; age, height-for-age z score, $ppFEV_1$, $ppFEV_1$ decile, FVC per cent predicted, FEV_1/FVC per cent predicted, FEF25-75 per cent predicted, dornase alfa, tobramycin, aztreonam, leukotriene modifiers, *Aspergillus*, *Alcaligenes*, *Burkholderia* species, methicillin-resistant *Staphylococcus aureus*, and methicillin-sensitive *Staphylococcus aureus*). Of note, any post-baseline FEV_1 values during the first 21 days of therapy were excluded from the analysis of the L400/IVA group.

Figure 20: Annual Rate of Change in $ppFEV_1$ — Registry Comparator Analysis



CFTR = cystic fibrosis transmembrane conductance regulator; CI = confidence interval; GLI = Global Lungs Function Initiative; h = hours; $ppFEV_1$ = per cent predicted forced expiratory volume in one second.

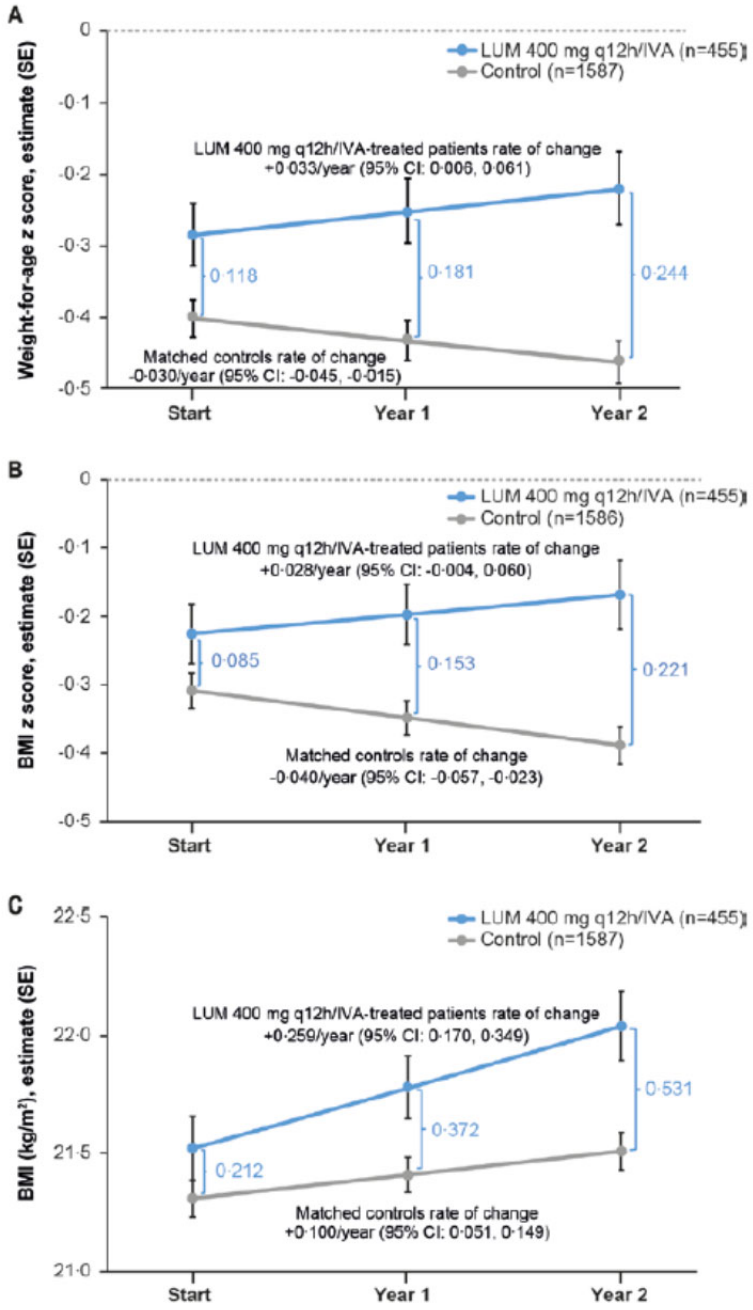
Note: Post-baseline data were limited to two years; visits occurring within the first 21 days of treatment were excluded.

Source: Reprinted from The Lancet Respiratory Medicine, 5(2), Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, et al., Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase III, extension study, 107-118, Copyright (2017), with permission from Elsevier.[31]

Body Mass Index and Body Weight

The annualized rate for change in weight-for-age z scores was 0.033; 95% CI 0.006 to 0.061 for the L400/IVA group and –0.030, 95% CI –0.045 to –0.015 for the registry control group, $P < 0.001$ (Table 62). As shown in Figure 21 A, there was no overlap between groups at the start of the study period and the groups continued to diverge. Similar trends were observed for the analysis of BMI as shown in Figure 21 B. The annualized rate for change in BMI z score was 0.028; 95% CI –0.004 to 0.050 for the L400/IVA group and –0.040; 95% CI –0.057 to –0.023 for the registry control group, $P < 0.001$. For the analysis of BMI, however, both groups showed a positive annualized rate of change (L400/IVA: 0.259; 95% CI, 0.170 to 0.349; registry control group: 0.100; 95% CI, 0.051 to 0.149, $P = 0.002$) (Figure 21 C).

Figure 21: Annual Rate of Change in Weight-For-Age Z Score (A), BMI Z Score (B), and BMI (C) — Registry Comparator Analysis



BMI = body mass index; CI = confidence interval; IVA = ivacaftor; LUM = lumacaftor; q12h = every 12 hours; SE = standard error.

Note: Post-baseline data were limited to two years; visits occurring within the first 21 days of treatment were excluded.

Source: Reprinted from The Lancet Respiratory Medicine, 5(2), Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, et al., Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase III, extension study, 107-118, Copyright (2017), with permission from Elsevier.[31]

Limitations

PROGRESS was an uncontrolled extension study that enrolled patients who had completed the 24-week pivotal TRAFFIC or TRANSPORT trials. The study evaluated two different dosing regimens of LUM/IVA, one of which was consistent with the Health Canada–approved dose (i.e., L400/IVA). Patients were blinded to the dose received, but would have known they were receiving active treatment, thus patients' perceptions and expectations of therapy could have biased the reporting of subjective outcomes, such as respiratory symptoms, or harms. Patients who were intolerant of LUM/IVA or were non-adherent to the drug or study protocol were excluded from PROGRESS (7%); thus, the study included patients who may be more likely to show a favourable treatment response. Attrition was substantial, with 42% of patients completing 96 weeks of treatment. Due to the frequency of withdrawals, the manufacturer truncated the analysis of efficacy outcomes at 72 weeks, at which time $ppFEV_1$ data were available for 75% of patients. All of the efficacy results should be interpreted with caution due to the substantial amount of missing end point data. It is likely patients reaching week 72 were fundamentally different in terms of benefits or AEs compared with patients who stopped the study earlier. Data on pulmonary exacerbations were based on a standard definition; however, events were not adjudicated by an independent committee. In addition, the study did not evaluate outcomes such as health-related quality of life or functional capacity, which are important to patients.

Konstan et al.[31] used propensity score methods to conduct a post hoc comparison between the clinical trial patients treated with L400/IVA, and control patients selected from the US CFFPR. This registry comparator analysis has a number of limitations related to the selection of patients and propensity score methods that may potentially bias the findings. With regards to patient selection, the CFFPR consists of US patients with CF that are treated in CF Foundation accredited centres and who have given consent to include their data in the registry. In contrast, TRAFFIC and TRANSPORT were multinational clinical trials, with approximately half of the patients enrolled from countries other than the US. Differences in outcomes have been reported in the literature between patients with CF in the US and other countries, with the US reporting lower median survival than Canada.[74] In addition, availability of medical insurance was not reported for the US registry patients. Use of active or preventive therapies for CF may have been impacted by insurance status, which could lead to worse outcomes compared with trial patients who received appropriate care irrespective of insurance status. The selection criteria for registry patients (age 12 years in 2012, homozygous for F508del, with valid race, sex, spirometry, and nutrition data from a stable encounter in 2012) were generally similar to the inclusion criteria used in the clinical trials. TRAFFIC and TRANSPORT, however, excluded patients with $ppFEV_1 < 40$ or > 90, or those with an exacerbation in the previous four weeks. Both the registry and clinical trial patients had to meet minimum follow-up criteria of at least three FEV_1 measurements over 0.5 years or more. The trial patients, however, were selected based on enrolment in the PROGRESS extension study, which excluded patients intolerant or non-adherent to LUM/IVA, and may represent patients more likely to show positive treatment effects. An additional 12% of patients were not matched to a control, and thus were excluded. It is not known if the characteristics of these patients were similar to patients who were included in the analysis.

Selection of patients and the generation of propensity scores are dependent on the availability of accurate demographic and clinical data, which may be a concern with registry-based analyses. The CFFPR has implemented a number of initiatives to improve data capture (e.g., Web-based portal with flags for values outside of expected ranges, key

fields require data to be entered) and provides funding to centres that is based on the number of patients enrolled and the completeness of their records. An audit of 2012 CFFPR data found that 5% of clinic visits and 10% of hospitalizations were missing.[125] Registry data matched the patient's medical records for > 82% of the records; however, medications prescribed were the least accurate, with antibiotic data showing lowest accuracy. CF mutation data were missing for 6% and inaccurate for 5% of records.[125] Moreover, it is estimated that 16% to 19% of US patients with CF are not included in the registry and their characteristics are unknown.[125] An analysis of patient attrition from 2009 to 2013 showed that those lost to follow-up (9%) or with gaps in data (5%) were older, more likely to receive a transplant, and less likely to have insurance than patients who had complete records.[125] As the data for the LUM/IVA group is taken from a clinical trial, which has more strict data quality requirements, the degree of missing or inaccurate data is not distributed equally across groups, and thus may bias the study.

The propensity scores were generated from logistic regression models that included variables identified as risk factors of lung function decline (see Table 58). Although three observational studies[95,119,120] were provided to support the selection of these variables, a number of potentially important confounders were not considered, such as exacerbation frequency[78,79,95,98] or socioeconomic status.[126,127] Many-to-one matching increases the sample size but may also increase bias from matches that are not as close to the initial match.[128] The balance diagnostic data reported were limited, and the authors concluded that groups were well matched, as the effect sizes for the distribution of baseline characteristics were less than 0.2. Although there is no universally agreed-upon threshold to indicate balance, some sources state that standardized differences less than 0.1 would represent negligible differences.[123] Seven of the variables had an effect size greater than 0.1, including $ppFEV_1$, tobramycin, aztreonam, and dornase alfa. Other important balance diagnostic data were not reported, such as box plots, cumulative density plots, or the distribution of variables by quintile of propensity scores. The balance across the full range of patients and important subgroups of patients were not presented; thus, whether balance was fully achieved and how this may have affected the study results is uncertainty. Moreover, approximately 19% of all patients dosed in TRAFFIC or TRANSPORT were not included in the matched analysis. How these patients relate to those included in the analysis in terms of characteristics and outcomes is unknown and exclusion of these patients may introduce bias into the study, particularly given that 7% were excluded for reasons related to $ppFEV_1$ data during follow-up. The study excluded patients who were unable to tolerate LUM/IVA or did not previously complete week 24 of TRANSPORT and TRAFFIC, thus the patients included may show a more favourable response to therapy than patients with CF in general. The results of the BMI z score, weight-for-age z score, and $ppFEV_1$ data further suggest there were imbalances between groups as the CIs did not overlap between groups at baseline. The manufacturer stated that the baseline differences are due to the exclusion of outcome data for the first 21 days in the LUM/IVA group.[122] Although treatment with LUM/IVA may increase $ppFEV_1$ shortly after the start of therapy, substantial changes in BMI or weight were not observed in LUM/IVA randomized controlled trials. Konstan et al.[31] have not provided sufficient evidence to support their claim that known confounders were balanced between groups. Furthermore, propensity score methods can only balance for measured confounders, and potential for confounding due to unknown or unmeasured confounders remains. An important difference exists between groups in their interaction with the health care system. Patients involved in a clinical trial receive a different level of care than routine practice and it is difficult to distinguish improved outcomes due to treatment compared with other health care the patients likely received.

The outcomes were analyzed using a mixed model with intercepts and slopes for each match group and patient-within-match group as random variables with unstructured covariances, and including the fixed effect for treatment group and age group (< 18 and ≥ 18 years). This model should appropriately account for correlation within-matched groups. The model assumed that the rate of decline in FEV_1 was constant over the observation period for each patient and no sensitivity analyses were conducted to test this major assumption using models where the rate of change was not expected to be constant.[122] It is not known what proportion of patients had outcome data at the end of the registry comparator analysis, but less than half of patients had $ppFEV_1$ data at the last PROGRESS visit. Thus, it is unclear if the number of patients and duration of follow-up was sufficient to generate robust estimates of the rate of change. Konstan et al.[31] stated that although the rate of decline of lung function for patients who received LUM/IVA was slower than the registry control group, causality cannot be definitively established as the patients who participate in clinical trials may differ systematically from those who do not.

With regards to external validity, the key issue is the comparison with a US cohort. There are a number of differences between the US and Canada with regards to the management of CF and US patients have a poorer prognosis compared with those in Canada.[74] As a result there are limitations to the generalizability of the findings from the registry cohort analysis.

Summary

PROGRESS was a phase III, multicenter, extension study that enrolled patients with CF 12 years of age and older who had completed 24 weeks in either the TRAFFIC or TRANSPORT clinical trials. All patients received L400/IVA or L600/IVA for up to 96 weeks during the extension period, with up to 120 weeks of therapy for those on active drug in the randomized controlled trials. Of the 516 patients who received L400/IVA in PROGRESS, 340 were on this dose in either TRAFFIC or TRANSPORT, and 176 patients had previously received placebo and started LUM/IVA on day one of the PROGRESS study.

No new safety signals were identified in PROGRESS. Infective pulmonary exacerbations were the most commonly reported AE (66%), followed by cough (51%), increased sputum (28%), hemoptysis (25%), dyspnea (22%), and headache (22%). The frequency of respiratory-related events was higher in the placebo patients who started LUM/IVA in PROGRESS (38%) than in the patients who continued on LUM/IVA during PROGRESS (29%). Ten per cent of patients stopped treatment due to AEs and 49% of patients experienced an SAE over the cumulative study period (up to 120 weeks).

The reported rate of pulmonary exacerbations was 0.65 events to 0.69 events per patient-year among patients who received L400/IVA in PROGRESS. An increase in $ppFEV_1$ was observed after initiation of LUM/IVA in TRAFFIC, TRANSPORT, or PROGRESS (least squares [LS] mean change from baseline to week 24 of 2.2% to 3.4%); however, at PROGRESS week 72, the LS mean change from baseline in $ppFEV_1$ had declined to 0.5% in the patients who continued L400/IVA since TRAFFIC and TRANSPORT, and 1.5% in patients who transitioned from placebo. The proportion of patients with ≥ 3% or ≥ 5% absolute change in $ppFEV_1$ also declined over time. BMI showed an increase over time, with a LS mean change from baseline of 0.69 kg/m^2 to 0.62 kg/m^2 at PROGRESS week 72, although the clinical importance of this increase is unclear given that the mean BMI was within the normal range at baseline. There was no net increase in BMI z scores for the subgroup of patients < 20 years of age at week 72, and CFQ-R respiratory domain results were difficult to interpret given the variability over time and potential bias (as patients were

aware of the treatment received). Efficacy data should be interpreted with caution given that this was an uncontrolled study that enrolled patients who were more likely to show a favourable response to treatment, and that the study had a substantial withdrawal rate at the later follow-up times.

A post hoc propensity score analysis was conducted by Konstan et al.[31] comparing patients with CF treated with L400/IVA with patients included in the US CFFPR. Patients from the PROGRESS extension study (N = 455) were matched with one to five patients at least 12 years of age who were homozygous for the F508del-CFTR and were included in the US registry (N = 1,588). The outcomes tested were the rate of change in the $ppFEV_1$, weight-for-age z score, BMI z score, and BMI. The analysis found differences between groups that favoured the clinical trial group over the registry control patients; however, these results should be interpreted with caution given the inherit limitations of the study design and conduct. A number of key limitations related to the selection of patients as well as the propensity score matching methods were identified that could potentially bias the results. First, the registry was limited to US patients, who may have less favourable outcomes than those from Canada.[74] Moreover, approximately one-fifth of all patients dosed in TRAFFIC or TRANSPORT were not included in the matched analysis and exclusion of these patients may introduce bias into the study. Second, the generation of propensity scores did not include important potential confounders, such as pulmonary exacerbation frequency and socioeconomic status, and may have been biased by the differential distribution of invalid or missing data between registry and clinical trial groups. Third, limited data were presented to support the authors' claims that the propensity score model was adequately specified and that patient characteristics were balanced between groups. The effect size data suggests there were some important differences in baseline characteristics, including $ppFEV_1$, and use of antibiotics and dornase alfa. Although the results of the registry comparator analysis showed the annualized rate of decline in $ppFEV_1$ was less in the L400/IVA-treated patients (–1.33%) than in controls (–2.29%), definitive conclusions regarding causality cannot be made. Propensity score methods can only control for measured confounders, and systematic differences may remain between the clinical trials patients and those selected from the registry.

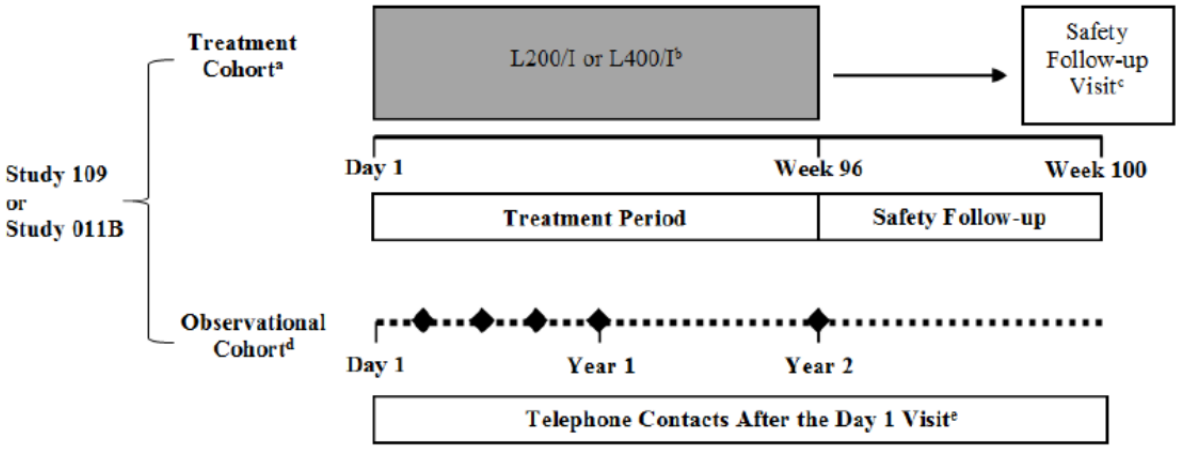
Appendix 7: Summary of Extension Study 110

The objective of this appendix is to provide a summary and critical appraisal of Study 110,[32] which evaluated the long-term safety, tolerability, and efficacy of lumacaftor 200 mg/ivacaftor 250 mg every 12 hour (L200/IVA) in patients aged six years and older with cystic fibrosis homozygous for the F508del-cystic fibrosis transmembrane conductance regulator mutation.

Study Design

Study 110 was a phase III, multicenter, open-label rollover study that included a treatment cohort and an observational cohort of patients who had previously participated in Study 109 or Study 11B (Figure 22). Data were available from an interim analysis (up to August 1, 2016) that included patients enrolled from Study 11B, all of whom had received at least 24 weeks of treatment in Study 110. No data were reported from patients who had previously participated in Study 109 in the interim report. Information from the observational group was excluded from this summary as this group's participants did not receive any dosing of L200/IVA. These patients were ineligible or declined to participate in the treatment cohort.

Figure 22: Schematic of Extension Study 110



L200/I = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; L400/I = lumacaftor 400 mg/ivacaftor 250 mg every 12 hours.

Source: Clinical study report.[32]

Patients aged six years and older with cystic fibrosis (CF), homozygous for the F508del-cystic fibrosis transmembrane conductance regulator mutation who completed 24 weeks of treatment in either Study 109 or Study 11B, or those who experienced study drug interruptions but completed study visits up to week 24 of Study 109 or week 26 in Study 11B, were eligible for enrolment in the treatment cohort. Patients who were not taking the study drug at the week 24 visit (including patients who required study drug interruption to be either continued or initiated at day 1 in Study 110) were required to have the manufacturer's approval for enrolment in the extension study. There was a planned two-week washout period between the end of treatment in Study 11B and enrolment in Study 110.
Patients who had turned 12 years of age before day 1 of Study 110 received lumacaftor 400 mg/ivacaftor 250 mg for up to 96 weeks and those less than 12 years of age received L200/IVA for up to 96 weeks.

The primary objective was to evaluate harms; secondary efficacy outcomes included change from baseline in lung clearance index, sweat chloride, body mass index (BMI), per cent predicted forced expiratory volume in one second ($ppFEV_1$), BMI z score, body weight, weight z score, height, and height z score. Data were also collected for the Cystic Fibrosis Questionnaire – Revised and pulmonary exacerbations but were not reported in the interim data analysis. Data for the lung clearance index data were incomplete (N = 25) and have not been included in this summary. Analyses were based on all available data with no imputation for missing data.

Patient Disposition

Of the 58 patients in Study 11B, 49 patients (84%) had enrolled in the extension study and were reported in the interim data analysis. At the interim data cut point, all but one patient were receiving the study drug. The patient who discontinued the study drug did so because of the availability of commercial lumacaftor/ivacaftor. The median exposure duration in Study 110 was 312 days (range: 237 to 354), with 90% of patients having received 24 to less than 48 weeks of treatment and 10% having received treatment for 48 weeks or longer in the interim data analysis (Table 64). For the cumulative study period (which included 58 patients with data from Study 11B and Study 110), the median treatment exposure was 492 days (range: 11 to 536).

Table 64: Exposure to Lumicaftor/Ivacaftor During Study 110

	Study 110 N = 49	Cumulative Study Period[a] N = 58
Total exposure in patient-years	45.4	75.7
Median exposure duration (days), (range)	312 (237 to 354)	492 (11 to 536)
Exposure duration, n (%)		
> 0 weeks to < 24 weeks	0	5 (9)
≥ 24 weeks to < 48 weeks	44 (90)	4 (7)
≥ 48 weeks to < 72 weeks	5 (10)	28 (48)
≥ 72 weeks to < 96 weeks	0	21 (36)
≥ 96 weeks	0	0

[a] Includes the time from the first study drug dose in Study 11B to the last dose in Study 110, regardless of treatment interruptions, the rollover gap between studies, and the planned two-week washout period between the two studies.

Source: Clinical study report.[30]

Baseline Characteristics

Half of the patients enrolled were female and all were white (Table 65). The mean $ppFEV_1$ was 90.9 and 45% of patients were positive for pseudomonas.

Table 65: Baseline Patient Characteristics from Study 110

Category	L200/IVA (N = 49)
Female, n (%)	25 (51)
Age (years)	
Mean (SD)	9.2 (1.5)
Median (range)	9 (6 to 11)
White, n (%)	49 (100)
Weight kg, Mean (SD)	31.7 (6.4)
Weight z score, Mean (SD)	–0.02 (1.07)
BMI, mean (SD)	16.8 (2.0)
BMI z score, mean (SD)	–0.04 (0.92)
$ppFEV_1$	
Mean (SD)	90.9 (13.6)
Min, max	55.0, 120.6
< 90, n (%)	23 (47)
≥ 90, n (%)	25 (51)
FEV_1 (L)	
Mean (SD)	1.68 (0.36)
Median (range)	1.67 (0.63 to 2.44)
Pseudomonas positive, n (%)	22 (45)

BMI = body mass index; FEV_1= forced expiratory volume in one second; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; max = maximum; min = minimum; $ppFEV_1$= per cent predicted forced expiratory volume in one second; SD = standard deviation.

Note: Based on baseline values from Study 011B.

Source: Clinical study report.[32]

Adverse Events

Nearly all patients (92%) reported an adverse event (AE) during Study 110, with infective pulmonary exacerbations (37%), cough (37%), nasal congestion (18%), and oropharyngeal pain (18%) reported most frequently (Table 66). Eight patients (16%) reported a serious adverse event (SAE), including infective pulmonary exacerbations of CF in six patients, and painful respiration, decreased pulmonary function test, or decreased oxygen saturation, which were each reported in one patient. No deaths were reported and no patients stopped treatment due to AEs. Elevated transaminase levels were reported in two patients (4%) and respiratory-related AEs were reported in four (8%).

Table 66: Adverse Events from Study 110

Adverse Events (Interim Analysis)	L200/IVA N = 49
Any adverse events, n (%)	45 (92)
Most common events (≥ 10%)	
Infective pulmonary exacerbation of CF	18 (37)
Cough	18 (37)
Nasal congestion	9 (18)
Oropharyngeal pain	9 (18)
Pyrexia	8 (16)
Abdominal pain, upper	7 (14)
Rhinorrhea	7 (14)
Bacterial test positive	7 (14)
Upper respiratory tract infection	5 (10)
Stopped treatment due to adverse events	0
SAEs	8 (16)
Deaths	0
Notable harms	
Elevated transaminases	2 (4)
Respiratory-related adverse events[a]	4 (8)
Cataracts	NR

CF = cystic fibrosis; L200/IVA = lumacaftor 200 mg/ivacaftor 250 mg every 12 hours; NR = not reported; SAE = serious adverse event.

[a] Included asthma, bronchial hyperreactivity, bronchospasm, chest discomfort, dyspnea, respiration abnormal, and wheezing.

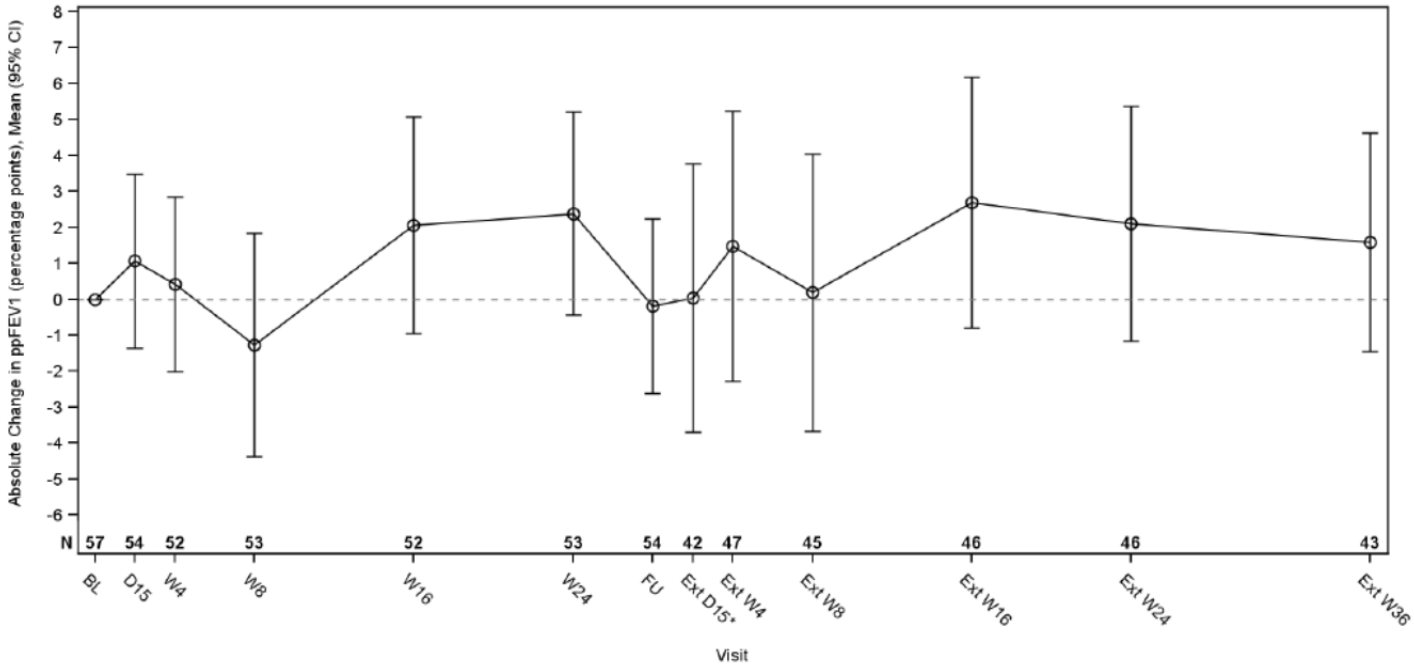
Source: Clinical study report.[32]

Efficacy

Forced Expiratory Volume in One Second

The mean $ppFEV_1$ at baseline was 90.9 (standard deviation [SD]: 13.6) for the patients who were enrolled in Study 110 (based on data from Study 11B). The absolute change from baseline in $ppFEV_1$ is reported in Figure 23 for the cumulative treatment duration starting in Study 11B and truncated at week 36 of the Study 110 extension phase. In Figure 23, the confidence intervals for the change in $ppFEV_1$ are wide and include the null value at each visit. Of note, at extension week 36, data were available for 43 patients, which was 88% of those who had enrolled in the extension (or 74% of those enrolled in Study 11B).

Figure 23: Absolute Change from Baseline in ppFEV$_1$ for Studies 11B and 110

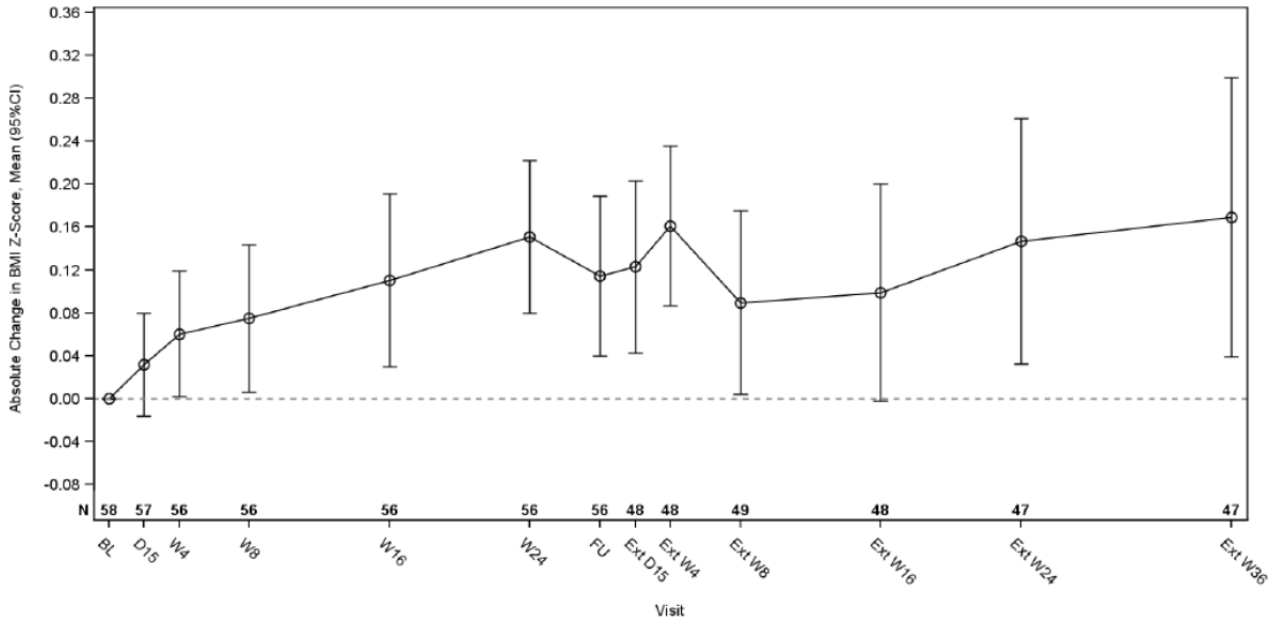


BL = baseline; CI = confidence interval; D = day; Ext. = extension phase; FU = follow-up; ppFEV$_1$= per cent predicted forced expiratory volume in one second; W = week.
Source: Clinical study report.[32]

Body Mass Index

The mean baseline BMI was 16.8 kg/m^2 (SD: 2.0) and the mean BMI z score was –0.04 (SD: 0.92). The absolute change from baseline in BMI z score is reported in Figure 24 for the cumulative treatment duration starting in Study 11B through to week 36 of the extension phase. The absolute change from baseline in BMI z score showed an increase over the course of Study 11B that appears to have been maintained during the extension period; however, the confidence intervals are wide, and at week 36 data were only available for 47 of the 58 patients who enrolled in the initial study (81%).

Figure 24: Absolute Change from Baseline in BMI Z Score for Studies 11B and 110



BL = baseline; BMI = body mass index; CI = confidence interval; D = day; Ext. = extension phase; FU = follow-up; W = week.
Source: Clinical study report.[32]

Limitations

The study was limited by the lack of a concurrent control group, its small sample size (49 patients), the extent of missing data (18% at week 36 for $ppFEV_1$), and its open-label design (which creates the potential to bias the reporting of harms). Moreover, the extension study excluded patients who were unable to tolerate L200/IVA or had poor adherence to treatment, thus the patients included may show a more favourable response to therapy than patients with CF in general.

Summary

The open-label extension study in patients with CF who were aged six years to 11 years showed no new safety signals with L200/IVA (total median treatment exposure of 492 days). Infective pulmonary exacerbations were the most commonly reported AE (37%) and SAE (12%). Other commonly reported AEs were cough (37%), nasal congestion (18%), oropharyngeal pain (18%), and pyrexia (16%). Data for the absolute change in $ppFEV_1$ and BMI z score showed similar results during the extension period as in the previous study period; however, these data should be interpreted with consideration given the limitations of the study (uncontrolled study, small sample size, open-label design, and the extent of missing data).

Appendix 8: Summary of F508del Mutation Testing

Materials 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; it is characterized as a class II defect.[129] Class II defects are among those associated with more severe manifestations of CF, and they result in complete loss of chloride channel function.[129] Cystic fibrosis transmembrane conductance regulator (CFTR) with the F508del mutation presents a deletion of three base pairs, involving the loss of an amino acid, phenylalanine, at position 508.[129] This results in a threefold problem that leads 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.[129] The second is that 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.[129] 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 of a normal CFTR protein.[129] According to the Canadian Cystic Fibrosis Registry, 50.0% of the 3,972 patients in the registry with CF were homozygous for F508del mutations and 89.7% of patients had at least one F508del mutation.[12]

Description of F508del Mutation Testing

DNA sequencing is considered the "gold standard" for DNA-based mutation testing.[130] However, for clinical laboratory settings, routine DNA sequencing is currently not practical or cost-effective for identifying CFTR gene mutations with more than 1,800 reported mutations in the CF gene.[131,132] 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.[130,133] The new ACMG panel of 23 mutations accounts for 94.04% of detectable mutations.[130] 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;[131] one panel included 106 mutations, which account for approximately 91% of CF genes in a Northern European Caucasian population.[134]

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, and oligonucleotide ligation assay (OLA)-PCR.[135] Commercially available CF testing platforms include eSensor CF carrier detection system, CF v3.0 OLA analyte-specific reagent (ASR), CFTR InPlex analyte-specific reagent (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.[135] Among these platforms, only Tag-It CF 40 + 4 is used in Canada (Tm Biosciences, Toronto, ON, Canada).[135] In one study,[135] Johnson et al. evaluated five CFTR testing platforms: 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 tests 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.[135] given that 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), as well as the criteria for the analytical and clinical validity of tests.[130]

Current Canadian Practice Regarding F508del Testing

The Canadian College of Medical Geneticists (CCMG) committee endorsed that CFTR mutation testing may be indicated for individuals or families at increased risk of CF due to considerations of family history or clinical manifestations.[136] The clinical expert consulted for this review confirmed that F508del mutation testing is part of the standard panel of mutations used in screening patients with CF. However, in terms of testing systems or platforms, no specific F508del-CFTR mutation testing recommendation was identified in the CCMG guideline (2011).[136] 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 patients with CF have had genotyping performed.[12]

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 system or platforms, no recommendation was identified in the CCMG guidelines (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.

References

1. Clinical Study Report: VX12-809-103. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous for the F508del-CFTR mutation [**CONFIDENTIAL** internal manufacturer's report]. Boston (MA): Vertex Pharmaceuticals Incorporated; 2014 Sep.
2. Clinical Study Report: VX12-809-104. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous for the F508del-CFTR mutation [**CONFIDENTIAL** internal manufacturer's report]. Boston (MA): Vertex Pharmaceuticals Incorporated; 2014 Sep.
3. 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 [supplementary appendix]. N Engl J Med. 2015 Jul 16;373(3):220-31.
4. Summary of clinical efficacy: module 2.7.4. In: CDR submission: Orkambi™ (lumacaftor/ivacaftor), tablets containing a fixed dose combination of 200mg lumacaftor and 125mg ivacaftor. Company: Vertex Pharmaceuticals (Canada) Incorporated [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Vertex Pharmaceuticals (Canada) Incorporated; 2016 Jan.
5. Vertex Pharmaceuticals Incorporated response to March 30, 2016 CDR request for additional information regarding the Orkambi CDR review: VX809 NDA ISE [**CONFIDENTIAL** internal manufacturer's report]. Boston (MA): Vertex Pharmaceuticals Incorporated; 2014 Jul 28.
6. Clinical Study Report: VX13-809-011. A phase 3, open-label study to evaluate the pharmacokinetics, safety, and tolerability of lumacaftor in combination with ivacaftor in subjects 6 through 11 years of age with cystic fibrosis, homozygous for the F508del-CFTR mutation [**CONFIDENTIAL** internal manufacturer's report]. Boston (MA): Vertex Pharmaceuticals Incorporated; 2016 Mar.
7. Clinical Study Report: VX14-809-109. A phase 3, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 6 through 11 years with cystic fibrosis, homozygous for the F508del-CFTR mutation [**CONFIDENTIAL** internal manufacturer's report]. Boston (MA): Vertex Pharmaceuticals Incorporated; 2017 Jan.
8. Clinical Study Report: VX15-809-112. A phase 4, randomized, double-blind, placebo-controlled, parallel-design study of the effect of lumacaftor/ivacaftor combination therapy on exercise tolerance in subjects aged 12 years and older with cystic fibrosis, homozygous for the F508del-CFTR mutation [**CONFIDENTIAL** internal manufacturer's report]. Boston (MA): Vertex Pharmaceuticals Incorporated; 2018 Apr.
9. Common Drug Review. CADTH Canadian Drug Expert Committee final recommendation: ivacaftor (Kalydeco - Vertex Pharmaceuticals (Canada) Incorporated). Indication: cystic fibrosis with G551D mutation [Internet]. Ottawa (ON): CADTH; 2013 Mar 22. [cited 2018 Jun 18]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Kalydeco_March-25-13_e.pdf
10. Common Drug Review. CADTH Canadian Drug Expert Committee final recommendation: ivacaftor (Kalydeco - Vertex Pharmaceuticals Inc.). Indication: cystic fibrosis with R117H mutation [Internet]. Ottawa (ON): CADTH; 2015 Nov 19. [cited 2018 Jun 18]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0430_complete_Kalydeco_R117H_Nov-23-15_e.pdf
11. Health Canada reviewer's report: Orkambi (lumcaftor/ivacaftor) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2015.
12. The Canadian Cystic Fibrosis Registry 2013 annual report. Toronto (ON): Cystic Fibrosis Canada; 2015 Jan.
13. Cystic Fibrosis Canada. The Canadian Cystic Fibrosis Registry: 2016 annual data report [Internet]. Toronto: Cystic Fibrosis Canada; 2017. [cited 2018 Apr 20]. Available from: http://www.cysticfibrosis.ca/uploads/2016%20Registry%20Annual%20Data%20Report.pdf
14. Lukacs GL, Verkman AS. CFTR: folding, misfolding and correcting the DeltaF508 conformational defect. Trends Mol Med [Internet]. 2012 Feb [cited 2018 Jun 18];18(2):81-91. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3643519
15. Okiyoneda T, Barriere H, Bagdany M, Rabeh WM, Du K, Hohfeld J, et al. Peripheral protein quality control removes unfolded CFTR from the plasma membrane. Science. 2010 Aug 13;329(5993):805-10.
16. Flume PA, O'Sullivan BP, Robinson KA, Goss CH, Mogayzel PJ, Jr., Willey-Courand DB, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. Am J Respir Crit Care Med [Internet]. 2007 Nov 15 [cited 2018 Jun 18];176(10):957-69. Available from: http://www.atsjournals.org/doi/pdf/10.1164/rccm.200705-664OC
17. Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. Pediatr Pulmonol. 2002 Aug;34(2):91-100.
18. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol [Internet]. 2001 Feb 15 [cited 2018 Jun 18];153(4):345-52. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2198936
19. Corey M, McLaughlin FJ, Williams M, Levison H. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. J Clin Epidemiol. 1988;41(6):583-91.
20. Cystic Fibrosis Foundation. Patient Registry. 2014 annual data report [Internet]. Bethesda (MD): The Foundation; 2015. [cited 2018 Jun 18]. Available from: https://www.cff.org/2014-Annual-Data-Report/
21. Cogen J, Emerson J, Sanders DB, Ren C, Schechter MS, Gibson RL, et al. Risk factors for lung function decline in a large cohort of young cystic fibrosis patients. Pediatr Pulmonol. 2015 Aug;50(8):763-70.
22. Mogayzel PJ, Jr., Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013 Apr 1;187(7):680-9.

23. Pencharz PB, Durie PR. Pathogenesis of malnutrition in cystic fibrosis, and its treatment. Clin Nutr. 2000 Dec;19(6):387-94.

24. Orkambi™ (lumacaftor/Ivacaftor): lumacaftor/Ivacaftor tablets 200 mg/125 mg [product monograph]. Laval (QC): Vertex Pharmaceuticals (Canada) Incorporated; 2016 Jan.

25. Committee for Medicinal Products for Human Use. Assessment report: Orkambi (lumacaftor/ivacaftor) [Internet]. London: European Medicines Agency; 2015 Sep. [cited 2018 Jun 18]. (European public assessment report). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003954/WC500197613.pdf

26. Common Drug Review. CADTH Canadian Drug Expert Committee final recommendation: lumacaftor/ivacaftor (Orkambi - Vertex Pharmaceuticals [Canada] Inc.). Indication: cystic fibrosis, F508del-CFTR mutation [Internet]. Ottawa (ON): CADTH; 2016. [cited 2018 Mar 23]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0471_complete_Orkambi-Oct-28-16.pdf

27. Common Drug Review. CADTH Canadian Drug Expert Committee final recommendation: ivacaftor (Kalydeco - Vertex Pharmaceuticals Inc.). Indication: cystic fibrosis with G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R mutation [Internet]. Ottawa (ON): CADTH; 2014 Dec 19. [cited 2018 Jun 18]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_SR0379_Kalydeco_Dec-23-14.pdf

28. Clinical Study Report: VX14-809-106. A phase 3b, open-label study to evaluate lumacaftor and ivacaftor combination therapy in subjects 12 years and older with cystic fibrosis and advanced lung disease, homozygous for the F508del-CFTR mutation [**CONFIDENTIAL** internal manufacturer's report]. Boston (MA): Vertex Pharmaceuticals Incorporated; 2017 Jan.

29. Taylor-Cousar JL, Jain M, Barto TL, Haddad T, Atkinson J, Tian S, et al. Lumacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease homozygous for F508del-CFTR. J Cyst Fibros [Internet]. 2017 Nov 7 [cited 2018 Apr 2];17:228-35. Available from: http://www.cysticfibrosisjournal.com/article/S1569-1993(17)30891-3/pdf

30. Clinical Study Report: VX12-809-105. A phase 3, rollover study to evaluate the safety and efficacy of long-term treatment with lumacaftor in combination with ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous or heterozygous for the F508del-CFTR mutation [**CONFIDENTIAL** internal manufacturer's report]. Boston (MA): Vertex Pharmaceuticals Incorporated; 2015 May.

31. Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. Lancet Respir Med. 2017;5(2):107-18.

32. Clinical Study Report: VX15-809-110. A phase 3, rollover study to evaluate the safety and efficacy of long-term treatment with lumacaftor in combination with ivacaftor in subjects aged 6 years and older with cystic fibrosis, homozygous for the F508del-CFTR mutation. Interim analysis 1 reports results for subjects in the study VX15-809-110 treatment cohort who previously participated in study VX13-809-011B [**CONFIDENTIAL** internal manufacturer's report]. Boston (MA): Vertex Pharmaceuticals Incorporated; 2017 Jan.

33. 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. N Engl J Med. 2015 Jul 16;373(3):220-31.

34. Summary of clinical efficacy: module 2.7.3. In: CDR submission: Orkambi™ (lumacaftor/ivacaftor), tablets containing a fixed dose combination of 200mg lumacaftor and 125mg ivacaftor. Company: Vertex Pharmaceuticals (Canada) Incorporated [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Vertex Pharmaceuticals (Canada) Incorporated; 2016 Jan.

35. Vertex Pharmaceuticals Incorporated. A study of lumacaftor in combination with ivacaftor in cystic fibrosis subjects aged 12 years and older who are homozygous for the F508del-CFTR mutation (TRAFFIC). 2016 Mar 4 [cited 2018 Jun 18; last updated 2015 Aug 31]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT01807923 Identifier: NCT01807923.

36. Vertex Pharmaceuticals Incorporated. A study of lumacaftor in combination with ivacaftor in cystic fibrosis subjects aged 12 years and older who are homozygous for the F508del-CFTR mutation (TRANSPORT). 2013 Mar 4 [cited 2018 Jun 18; last updated 2016 Sep 27]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT01807949 Identifier: NCT01807949.

37. Vertex Pharmaceuticals Incorporated. A study of the effects of lumacaftor/ivacaftor on exercise tolerance in subjects with cystic fibrosis, homozygous for the F508del-CFTR mutation. 2017 Dec 2 [cited 2018 Apr 23; last updated 2017 Dec 2]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02875366 NLM Identifier: NCT02875366.

38. Ratjen F, Hug C, Marigowda G, Tian S, Huang X, Stanojevic S, et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. Lancet Respir Med. 2017;5(7):557-67.

39. Milla CE, Ratjen F, Marigowda G, Liu F, Waltz D, Rosenfeld M, et al. Lumacaftor/ivacaftor in patients aged 6-11 years with cystic fibrosis and homozygous for F508del-CFTR. Am J Resp Crit Care Med [Internet]. 2017 [cited 2018 Apr 2];195(7):912-20. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5440888/pdf/rccm.201608-1754OC.pdf

40. National Institute for Health and Care Excellence. Appraisal consultation document: lumacaftor-ivacaftor for treating cystic fibrosis homozygous for the F508del mutation [Internet]. London: The Institute; 2016. [cited 2018 Jun 18]. Available from: https://www.nice.org.uk/guidance/GID-TAG530/documents/appraisal-consultation-document

41. Vertex Pharmaceuticals Incorporated. Study of lumacaftor in combination with ivacaftor in subjects 6 through 11 years of age with cystic fibrosis, homozygous for the F508del-CFTR mutation. 2013 Jul 8 [cited 2018 Jun 18; last updated 2017 Jun 20]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT01897233 Identifier: NCT01897233.

42. Vertex Pharmaceuticals Incorporated. A study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects with CF, homozygous for the F508del-CFTR mutation. 2015 Jul 23 [cited 2018 Jun 18; last updated 2017 Oct 23]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02514473 Identifier: NCT02514473.

43. Clinical value of ORKAMBI (lumacaftor/ivacaftor) for the treatment of cystic fibrosis (CF) in patients 6 years of age and older who are homozygous for the *F508* deletion mutation in the *CFTR* gene. In: CDR submission: Orkambi (lumacaftor/ivacaftor) pediatric, 100 mg/125 mg, 200 mg/125 mg tablets. Company: Vertex Pharmaceuticals (Canada) Incorporated [**CONFIDENTIAL** manufacturer's submission]. Toronto (ON): Vertex Pharmaceuticals (Canada) Incorporated; 2018 Feb 22. Toronto: Vertex Pharmaceuticals (Canada) Incorporated; 2018.

44. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG, Jr. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol. 1993 Feb;15(2):75-88.

45. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999 Jan;159(1):179-87.

46. Subbarao P, Milla C, Aurora P, Davies JC, Davis SD, Hall GL, et al. Multiple-breath washout as a lung function test in cystic fibrosis. A Cystic Fibrosis Foundation workshop report. Ann Am Thorac Soc [Internet]. 2015 Jun [cited 2018 Apr 12];12(6):932-9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5466249/pdf/AnnalsATS.201501-021FR.pdf

47. Kent L, Reix P, Innes JA, Zielen S, Le BM, Braggion C, et al. Lung clearance index: evidence for use in clinical trials in cystic fibrosis. J Cyst Fibros. 2014 Mar;13(2):123-38.

48. Human Medicines Development and Evaluation. Report of the workshop on endpoints for cystic fibrosis clinical trials [Internet]. London (GB): European Medicines Agency; 2012. [cited 2018 Apr 20]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/12/WC500136159.pdf

49. Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. Chest [Internet]. 2009 Jun [cited 2018 Apr 17];135(6):1610-8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2821291/pdf/zcb1610.pdf

50. Sinnot PL, Joyce VR, Barnett PG. Guidebook: preference measurement in economic analysis [Internet]. Menlo Park (CA): Health Economics Resource Center (HERC); 2007 Mar. [cited 2018 Jun 18]. Available from: http://www.herc.research.va.gov/files/BOOK_419.pdf

51. van Reenen M, Oppe M. EQ-5D-3L user guide: basic information on how to use the EQ-5D-3L instrument. Version 5.1. Rotterdam, The Netherlands: EuroQol Research Foundation; 2015.

52. Vertex Pharmaceuticals Incorporated response to March 30, 2016 CDR request for additional information regarding the Orkambi CDR review: Lumacaftor (VX-809) CTD Statistical Analysis Plan [**CONFIDENTIAL** internal manufacturer's report]. Boston (MA): Vertex Pharmaceuticals Incorporated; 2014 May 9.

53. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s). In: Orkambi (lumacaftor/ivacaftor) oral tablet. Company: Vertex Pharmaceuticals, Inc. Application No.: 206038. Approval Date: 07/02/2015 [Internet]. Rockville (MD): FDA; 2015 Jul 2 [cited 2018 Jun 18]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/0206038Orig1s000TOC.cfm

54. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s). In: Orkambi (lumacaftor/ivacaftor) oral tablet. Company: Vertex Pharmaceuticals, Inc. Application No.: 206038. Approval Date: 07/02/2015 [Internet]. Rockville (MD): FDA; 2015 Jul 2 [cited 2018 Jun 18]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/0206038Orig1s000TOC.cfm

55. Flume PA, Liou TG, Borowitz DS, Li H, Yen K, Ordonez CL, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. Chest [Internet]. 2012 Sep [cited 2018 Jun 18];142(3):718-24. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3435140

56. Vertex Pharmaceuticals Incorporated. Study of ivacaftor in cystic fibrosis subjects aged 12 years and older homozygous for the F508del-CFTR mutation (DISCOVER). 2015 [cited 2018 Jun 18; last updated: 2015 Sep 11]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/results/NCT00953706 Identifier: NCT00953706.

57. Committe for Medicinal Products for Human Use. Assessment report: Orkambi (lumacaftor/ivacaftor) [Internet]. London: European Medicines Agency; 2017. [cited 2018 Mar 23]. (European public assessment report). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/003954/WC500241753.pdf

58. Vertex Pharmaceuticals Incorporated. Study to evaluate lumacaftor and ivacaftor combination therapy in subjects 12 years and older with advanced lung disease. 2015 Mar 11 [cited 2018 Jun 18; last updated 2017 Dec 6]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02390219 Identifier:NCT02390219.

59. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med [Internet]. 2011 Nov 3 [cited 2018 Jun 18];365(18):1663-72. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3230303/pdf/nihms338788.pdf

60. Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. Am J Respir Crit Care Med [Internet]. 2013 Jun 1 [cited 2018 Jun 18];187(11):1219-25. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3734608/pdf/rccm.201301-0153OC.pdf

61. Vertex Pharmaceuticals Incorporated. Study of ivacaftor in subjects with cystic fibrosis (CF) who have a non-G551D CF transmembrane conductance regulator (CFTR) gating mutation (KONNECTION). 2012 Jun 5 [cited 2018 Jun 18; last updated: 2014 Oct 29]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT01614470 Identifier: NCT01614470.

62. Vertex Pharmaceuticals Incorporated. Study of ivacaftor in subjects with cystic fibrosis (CF) who have the R117H-CF transmembrane conductance regulator (CFTR) gating mutation (KONDUCT). 2012 Jun 5 [cited 2018 Jun 18; last updated: 2015 Feb 12]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT01614457 Identifier: NCT01614457.

63. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. Eur Respir J. 2005 Jul;26(1):153-61.

64. Considerations for the use of lumacaftor and ivacaftor fixed dose combination oral tablets (Orkambi™) for the management of persons with cystic fibrosis and two F508del CFTR mutations [Internet]. Bethesda (MD): Cystic Fibrosis Foundation; 2015 Aug 28. [cited 2018 Jun 18]. Available from: https://www.cff.org/PDF-Archive/Orkambi-Whitepaper/

65. Single technology appraisal: lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786] [Internet]. London: National Institute for Health and Care Excellence; 2016. [cited 2018 Jun 18]. Available from: https://www.nice.org.uk/guidance/GID-TAG530/documents/committee-papers

66. Siracusa CM, Ryan J, Burns L, Wang Y, Zhang N, Clancy JP, et al. Electronic monitoring reveals highly variable adherence patterns in patients prescribed ivacaftor. J Cyst Fibros. 2015 Sep;14(5):621-6.

67. Health Canada reviewer's report: Orkambi (lumacaftor/ivacaftor) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2017 Apr 1.

68. Committee for Medicinal Products for Human Use. Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006: Orkambi (lumacaftor/ivacaftor0 [Internet]. London: European Medicines Agency; 2017. [cited 2018 Mar 23]. (European public assessment report). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/003954/WC500240951.pdf

69. Cystic Fibrosis Canada [Internet]. Toronto; 2016. The Canadian CF registry; 2013 [cited 2018 Jun 18]. Available from: http://www.cysticfibrosis.ca/cf-care/cf-registry

70. Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation [Internet]. London (GB): National Institute for Health and Care Excellence (NICE); 2016. [cited 2018 Jun 8]. (Technology appraisal guidance; no.TA398). Available from: https://www.nice.org.uk/guidance/ta398/resources/lumacaftorivacaftor-for-treating-cystic-fibrosis-homozygous-for-the-f508del-mutation-pdf-82602916891333

71. Pharmaceutical Benefit Advisory Committee. Public summary document: lumacaftor and ivacaftor: tablet containing lumacaftor 200 mg with ivacaftor 125 mg Orkambi® [Internet]. Canberra (AU): Pharmaceutical Benefits Scheme; 2017. [cited 2018 Jun 15]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2017-07/files/lumacaftor-ivacaftor-psd-july-2017.pdf

72. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Summary review. In: Orkambi (lumacaftor/ivacaftor). Company: Vertex Pharmaceuticals, Inc. Application no.: 206038. Approval date: 07/02/2015 [Internet]. Rockville (MD): FDA; 2015 Jun 25 [cited 2018 Jun 18]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/0206038Orig1s000SumR.pdf

73. Health Canada [Internet]. Ottawa (ON): Health Canada; 2016. Orkambi: summary basis of decision; 2016 [cited 2018 Jun 18]. Available from: https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00294

74. Goss CH, Sykes J, Stanojevic S, Marshall B, Petren K, Ostrenga J, et al. Comparison of nutrition and lung function outcomes in patients with cystic fibrosis living in Canada and the United States. Am J Respir Crit Care Med. 2018 Mar 15;197(6):768-75.

75. Pharmaceutical Benefit Advisory Committee. Public summary document: lumacaftor with ivacaftor: tablet containing lumacaftor 200 mg with ivacaftor 125 mg Orkambi® [Internet]. Canberra (AU): Pharmaceutical Benefits Scheme; 2016. [cited 2018 Apr 24]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-11/files/lumacaftor-ivacaftor-psd-november-2016.pdf

76. Modulator treatments for cystic fibrosis: effectiveness and value. Final evidence report and meeting summary [Internet]. Boston (MA): Institute for Clinical and Economic Review; 2018 Mar 15. [cited 2018 Jun 15]. Available from: https://icer-review.org/wp-content/uploads/2017/10/CF_Final_Evidence_Report_06072018.pdf

77. Bhatt JM. Treatment of pulmonary exacerbations in cystic fibrosis. Eur Respir Rev [Internet]. 2013 Sep 1 [cited 2018 Jun 18];22(129):205-16. Available from: http://err.ersjournals.com/content/22/129/205.long

78. de Boer K, Vandemheen KL, Tullis E, Doucette S, Fergusson D, Freitag A, et al. Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis. Thorax. 2011 Aug;66(8):680-5.

79. Waters V, Stanojevic S, Atenafu EG, Lu A, Yau Y, Tullis E, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. Eur Respir J. 2012 Jul;40(1):61-6.

80. Waters V, Atenafu EG, Salazar JG, Lu A, Yau Y, Matukas L, et al. Chronic stenotrophomonas maltophilia infection and exacerbation outcomes in cystic fibrosis. J Cyst Fibros. 2012 Jan;11(1):8-13.

81. Solem CT, Vera-Llonch M, Liu S, Botteman M, Castiglione B. Impact of pulmonary exacerbations and lung function on generic health-related quality of life in patients with cystic fibrosis. Health Qual Life Outcomes [Internet]. 2016 [cited 2018 Jun 18];14(1):63. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4839094

82. Sanders DB, Bittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. Am J Respir Crit Care Med [Internet]. 2010 Sep 1 [cited 2018 Jun 18];182(5):627-32. Available from: http://www.atsjournals.org/doi/pdf/10.1164/rccm.200909-1421OC

83. Sanders DB, Hoffman LR, Emerson J, Gibson RL, Rosenfeld M, Redding GJ, et al. Return of FEV1 after pulmonary exacerbation in children with cystic fibrosis. Pediatr Pulmonol. 2010 Feb;45(2):127-34.

84. Cystic Fibrosis Canada's CF Physician Panel on lumacaftor/ivacaftor: recommendations for criteria for clinical use [Internet]. Toronto (ON): Cystic Fibrosis Canada; [cited 2018 Jun 14]. Available from: https://www.cysticfibrosis.ca/uploads/advocacy/clinical%20criteria%20endorsements-FINAL.pdf

85. Ren CL, Morgan RL, Oermann C, Resnick HE, Brady C, Campbell A, et al. Cystic Fibrosis Foundation pulmonary guidelines. Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. Ann Am Thorac Soc. 2018;15(3):271-80.

86. Institute for Quality and Efficiency in Health Care. Lumacaftor/ivacaftor (cystic fibrosis) - benefit assessment according to §35a Social Code Book V. Köln (DE): The Institute; 2018.

87. European Medicines Agency. Summary of the risk management plan (RMP) for Orkambi (lumacaftor and ivacaftor) [Internet]. London: The Agency; 2015. [cited 2018 Jun 18]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Risk-management-plan_summary/human/003954/WC500194320.pdf

88. Scottish Medicines Consortium. lumacaftor 200mg, ivacaftor 125mg film-coated tablet (Orkambi®) [Internet]. Glasgow: Scottish Medicines Consortium; 2016. [cited 2018 Jun 18]. Available from: http://www.scottishmedicines.org.uk/files/advice/lumacaftor-ivacaftor__Orkambi__FINAL_April_2016_for_website.pdf

89. Pharmaceutical Benefit Advisory Committee. March 2016 PBAC outcomes - 1st time decision to not recommend: Orkambi [Internet]. Canberra (AU): Pharmaceutical Benefits Scheme; 2016 Mar 1. [cited 2018 Jun 18]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2016-03/first-time-decisions-not-to-recommend-2016-03.pdf

90. Pharmaceutical Benefit Advisory Committee. July 2018 PBAC Meeting - positive recommendations [Internet]. Canberra (AU): Pharmaceutical Benefits Scheme; 2018 Jul. [cited 2018 Aug 23]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2018-07/positive-recommendations-07-2018.pdf

91. Nutzenbewertungsverfahren zum Wirkstoff Lumacaftor/Ivacaftor (neues Anwendungsgebiet: Patienten ab 6 Jahren) [Internet]. Berlin: Gemeinsamer Bundesausschuss; 2018. [cited 2018 Aug 23]. Available from: https://www.g-ba.de/informationen/nutzenbewertung/344/#tab/zweckmaessige-vergleichstherapie In German.

92. Vertex Pharmaceuticals (Canada) Incorporated comments on CDR review [**CONFIDENTIAL** additional manufacturer's information]. Toronto (ON): Vertex Pharmaceuticals (Canada) Incorporated; 2018 Jun.

93. News release, Vertex announces long-term access agreement in Sweden for cystic fibrosis medicine Orkambi® (lumacaftor/ivacaftor) [Internet]. Boston (MA): Vertex Pharmaceuticals Incorporated; 2018 Jun 18. [cited 2018 Jun 21]. Available from: https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-long-term-access-agreement-sweden-cystic

94. Symdeko (tezacaftor / ivacaftor tablets and ivacaftor tablets): tezacaftor 100 mg / ivacaftor 150 mg tablets and ivacaftor 150 mg tablets, oral [product monograph] [Internet]. Toronto (ON): Vertex Pharmaceuticals (Canada) Incorporated; 2018 Jun 27. [cited 2018 Aug 24]. Available from: https://pdf.hres.ca/dpd_pm/00046145.PDF

95. Konstan MW, Morgan WJ, Butler SM, Pasta DJ, Craib ML, Silva SJ, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. J Pediatr. 2007 Aug;151(2):134-9.

96. Konstan MW, Wagener JS, Pasta DJ, Millar SJ, Jacobs JR, Yegin A, et al. Clinical use of dornase alpha is associated with a slower rate of FEV1 decline in cystic fibrosis. Pediatr Pulmonol [Internet]. 2011 Jun [cited 2018 Jun 18];46(6):545-53. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4109161

97. Sawicki GS, Signorovitch JE, Zhang J, Latremouille-Viau D, von WM, Wu EQ, et al. Reduced mortality in cystic fibrosis patients treated with tobramycin inhalation solution. Pediatr Pulmonol. 2012 Jan;47(1):44-52.

98. Stephenson AL, Tom M, Berthiaume Y, Singer LG, Aaron SD, Whitmore GA, et al. A contemporary survival analysis of individuals with cystic fibrosis: a cohort study. Eur Respir J. 2015 Mar;45(3):670-9.

99. Waters V, Ratjen F. Pulmonary exacerbations in children with cystic fibrosis. Ann Am Thorac Soc. 2015 Nov;12 Suppl 2:S200-S206.

100. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005 Aug;26(2):319-38.

101. Committe for Medicinal Products for Human Use. Guideline on the clinical development of medicinal products for the treatment of cystic fibrosis [Internet]. London, UK: European Medicines Agency; 2008 May 30. [cited 2018 Jun 18]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003507.pdf

102. Issues in the design of clinical trials of aerosolized antimicrobials for the treatment of cystic fibrosis. Day 2: efficacy endpoints for clinical trials of aerolised antimicrobials. Silver Spring (MD): U.S. Food and Drug Administration; 2010 Sep 23.

103. Robinson PD, Latzin P, Verbanck S, Hall GL, Horsley A, Gappa M, et al. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. Eur Respir J. 2013 Mar;41(3):507-22.

104. Hatziagorou E, Avramidou V, Kirvassilis F, Tsanakas J. Use of lung clearance index to assess the response to intravenous treatment in cystic fibrosis. Hippokratia [Internet]. 2015 Jan [cited 2018 Apr 12];19(1):47-52. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4574587/pdf/hippokratia-19-47.pdf

105. Welsh L, Nesci C, Tran H, Tomai M, Ranganathan S. Lung clearance index during hospital admission in school-age children with cystic fibrosis. J Cyst Fibros [Internet]. 2014 Dec [cited 2018 Apr 12];13(6):687-91. Available from: http://www.cysticfibrosisjournal.com/article/S1569-1993(14)00118-0/pdf

106. Vermeulen F, Proesmans M, Boon M, Havermans T, De BK. Lung clearance index predicts pulmonary exacerbations in young patients with cystic fibrosis. Thorax. 2014 Jan;69(1):39-45.

107. Stanojevic S, Davis SD, Retsch-Bogart G, Webster H, Davis M, Johnson RC, et al. Progression of lung disease in preschool patients with cystic fibrosis. Am J Respir Crit Care Med. 2017 May 1;195(9):1216-25.

108. Oude EE, Ratjen F, Davis SD, Retsch-Bogart G, Amin R, Stanojevic S. Inter-test reproducibility of the lung clearance index measured by multiple breath washout. Eur Respir J [Internet]. 2017 Oct [cited 2018 Apr 12];50(4). Available from: http://erj.ersjournals.com/content/erj/50/4/1700433.full.pdf

109. Poncin W, Singer F, Aubriot AS, Lebecque P. Agreement between multiple-breath nitrogen washout systems in children and adults. J Cyst Fibros. 2017 Mar;16(2):258-66.

110. Grosse-Onnebrink J, Mellies U, Olivier M, Werner C, Stehling F. Chest physiotherapy can affect the lung clearance index in cystic fibrosis patients. Pediatr Pulmonol. 2017 May;52(5):625-31.

111. Henry B, Aussage P, Grosskopf C, Goehrs JM. Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. Qual Life Res. 2003 Feb;12(1):63-76.

112. Tluczek A, Becker T, Grieve A, Laxova A, Rock MJ, Gershan WM, et al. Health-related quality of life in children and adolescents with cystic fibrosis: convergent validity with parent-reports and objective measures of pulmonary health. J Dev Behav Pediatr [Internet]. 2013 May [cited 2018 Apr 12];34(4):252-61. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3775595/pdf/nihms464861.pdf

113. Quittner AL, Sawicki GS, McMullen A, Rasouliyan L, Pasta DJ, Yegin A, et al. Erratum to: psychometric evaluation of the Cystic Fibrosis Questionnaire-Revised in a national, US sample. Qual Life Res. 2012 Sep;21(7):1279-90.

114. Retsch-Bogart GZ, Quittner AL, Gibson RL, Oermann CM, McCoy KS, Montgomery AB, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. Chest [Internet]. 2009 May [cited 2018 Jun 18];135(5):1223-32. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2818415

115. Modi AC, Quittner AL. Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. J Pediatr Psychol. 2003 Dec;28(8):535-45.

116. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of the Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. Chest. 2005 Oct;128(4):2347-54.

117. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199-208.

118. Brooks R. EuroQol: the current state of play. Health Policy. 1996 Jul;37(1):53-72.

119. Konstan MW, Wagener JS, VanDevanter DR, Pasta DJ, Yegin A, Rasouliyan L, et al. Risk factors for rate of decline in FEV1 in adults with cystic fibrosis. J Cyst Fibros [Internet]. 2012 Sep [cited 2018 May 3];11(5):405-11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4086189/pdf/nihms-603903.pdf

120. Schaedel C, de M, I, Hjelte L, Johannesson M, Kornfalt R, Lindblad A, et al. Predictors of deterioration of lung function in cystic fibrosis. Pediatr Pulmonol. 2002 Jun;33(6):483-91.

121. Millar SJ, Pasta DJ. The last shall be first: matching patients by choosing the least popular first. In: SAS Conference Proceedings: Western Users of SAS Software 2010; 2010 Nov 3-5; San Francisco, CA. San Francisco (CA): SAS Institute Inc.; 2010.

122. Vertex Pharmaceuticals (Canada) Incorporated response to May 9, 2018 CDR request for additional information regarding the Orkambi (lumacaftor/ivacaftor) pediatric CDR review: the registry comparator analysis methods and results [**CONFIDENTIAL** additional manufacturer's information]. Toronto (ON): Vertex Pharmaceuticals (Canada) Incorporated; 2018 May.

123. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res [Internet]. 2011 May [cited 2018 Jun 18];46(3):399-424. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3144483

124. Austin PC. Assessing balance in measured baseline covariates when using many-to-one matching on the propensity-score. Pharmacoepidemiol Drug Saf. 2008 Dec;17(12):1218-25.

125. Knapp EA, Fink AK, Goss CH, Sewall A, Ostrenga J, Dowd C, et al. The Cystic Fibrosis Foundation Patient Registry. Design and methods of a National Observational Disease Registry. Ann Am Thorac Soc. 2016 Jul;13(7):1173-9.

126. Schechter MS, Shelton BJ, Margolis PA, Fitzsimmons SC. The association of socioeconomic status with outcomes in cystic fibrosis patients in the United States. Am J Respir Crit Care Med. 2001 May;163(6):1331-7.

127. Ong T, Schechter M, Yang J, Peng L, Emerson J, Gibson RL, et al. Socioeconomic status, smoke exposure, and health outcomes in young children with cystic fibrosis. Pediatrics. 2017 Feb;139(2).

128. Garrido MM, Kelley AS, Paris J, Roza K, Meier DE, Morrison RS, et al. Methods for constructing and assessing propensity scores. Health Serv Res [Internet]. 2014 Oct [cited 2018 Jun 18];49(5):1701-20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4213057

129. Rodrigues R, Gabetta CS, Pedro KP, Valdetaro F, Fernandes MI, Magalhaes PK, et al. Cystic fibrosis and neonatal screening. Cad Saude Publica [Internet]. 2008 [cited 2018 Jun 18];24 Suppl 4:s475-s484. Available from: http://www.scielo.br/pdf/csp/v24s4/02.pdf

130. American College of Medical Genetics. Standards and guidelines for clinical genetics laboratories [Internet]. Bethesda (MD): The College; 2008. [cited 2018 Jun 18; revised 2011 Mar]. Available from: https://www.acmg.net/StaticContent/SGs/CFTR%20Mutation%20Testing.pdf

131. Chiarot J, Lands LC. Diagnostic aspects of cystic fibrosis. Canadian Journal of Diagnosis [Internet]. 2001 [cited 2018 Jun 18];94-101. Available from: http://www.stacommunications.com/journals/diagnosis/2001/12_December/cff.pdf

132. Patient registry: 2011 annual data report. Bethesda (MD): Cystic Fibrosis Foundation; 2012.

133. Update on carrier screening for cystic fibrosis. Washington (DC): American Congress of Obstetricians and Gynecologists; 2011. (Committee opinion, no. 486).

134. Mayo Medical Laboratories. Test ID: CFP: cystic fibrosis mutation analysis, 106- mutation panel [Internet]. Rochester (MN): The Laboratories; 2015. [cited 2018 Jun 18]. Available from: http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/35386

135. Johnson MA, Yoshitomi MJ, Richards CS. A comparative study of five technologically diverse CFTR testing platforms. J Mol Diagn [Internet]. 2007 Jul [cited 2018 Jun 18];9(3):401-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1899413

136. CCMG Molecular Genetics Committee. Canadian College of Medical Geneticists - CF testing/screening guidelines [Internet]. Ottawa: Canadian College of Medical Geneticists; 2011. [cited 2018 Jun 18]. Available from: http://www.ccmg-ccgm.org/images/CCMG_PractGuid_MOL_CF_Testing_20Jan2011.pdf