Common Drug Review
Clinical Review Report

July 2015

Drug	ivacaftor (Kalydeco) 150 mg tablet
Indication	For treatment of cystic fibrosis (CF) in patients age six years and older who have one of the following mutations in the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R.
Listing request	As per indication
Manufacturer	Vertex Pharmaceuticals Incorporated

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ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate transaminase
BMI	body mass index
CDR	Common Drug Review
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator
CI	confidence interval
DB	double blind
EQ-5D	EuroQol Questionnaire
FAS	full analysis set
FDA	Food and Drug Administration
FEV$_1$	forced expiratory volume in one second
GGT	gamma-glutamyl transpeptidase
ITT	intention-to-treat population
IV	intravenous
IVA	ivacaftor
LMM	linear mixed model
LOCF	last observation carried forward
LS	least square
MCID	minimal clinically important difference
MMRM	mixed model repeated measure
NA	not applicable
NR	not reported
PL	placebo
PPS	per-protocol set
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SoC	standard of care
vs.	versus
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Cystic fibrosis (CF), an autosomal recessive condition,[1] is the most common fatal genetic disease affecting children and young adults in Canada.[2] It is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, located on chromosome seven. This gene encodes for a chloride channel that regulates transport of salt and water across cell membranes. When CFTR is dysfunctional, secretions become tenacious and sticky, resulting in pathology in multiple organ systems, most notably the lungs and gastrointestinal tract.

Although there is no cure for the underlying disease process, current therapies have increased the overall survival of CF patients, with the median life expectancy now at 48 years based on recent Canadian statistics.[3] The goals of CF therapy until now have been: (1) preservation of lung function by minimizing pulmonary infection and inflammation; (2) restoration of baseline pulmonary function, symptoms, and level of inflammation following acute respiratory exacerbations; and (3) maintenance of adequate nutrition. Therapeutic strategy consists of a combination of physiotherapy, pharmacologic drugs (i.e., antibiotics, anti-inflammatory drugs, mucolytic drugs), nutritional treatments (i.e., high-calorie and high-fat diets)[4] and pancreatic enzyme replacement for those with pancreatic insufficiency. To date, no therapies have addressed the underlying genetic defect or corrected the abnormal functioning of CFTR.

Ivacaftor is a first-in-class oral CFTR potentiator approved by Health Canada for the treatment of CF in patients aged six years and older who have G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R mutation in the CFTR gene. The drug works by prolonging the time that activated CFTR channels remain open, thereby enhancing the regulation of chloride and water transport across cell membranes.[5] It is available as a 150 mg oral tablet. The Health Canada recommended dose is 150 mg every 12 hours with fat-containing food. The manufacturer is seeking a listing recommendation based on the Health Canada indication.

Accordingly, a systematic review was undertaken to evaluate the beneficial and harmful effects of ivacaftor 150 mg for the treatment of CF in patients age six years and older who have a G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R mutation in the CFTR gene.

Results and Interpretation

Included Studies

The evidence for this review comes from three phase 3, double-blind, randomized, placebo-controlled studies (KONNECTION, STRIVE, and ENVISION), together comprising 251 patients with CF of mild to moderate severity (forced expiratory volume in one second [FEV_1] ≥ 40% predicted) and specific gating mutations. KONNECTION included patients without a G551D mutation and with one of the following mutations in at least one allele: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R. STRIVE and ENVISION included patients with a G551D mutation in at least one allele. KONNECTION and STRIVE both included a mixed population of pediatric and adult patients and ENVISION included only pediatric patients. KONNECTION was a crossover study of 20 to 24 weeks' duration comprised of ivacaftor or placebo for eight weeks, followed by a four to eight week washout period followed by crossover to an additional eight weeks of ivacaftor or placebo. Both STRIVE and ENVISION had a duration of 48 weeks. In all three studies the ivacaftor dose was a 150 mg tablet once every 12 hours and patients were recommended to continue with their stable medications for CF except

hypertonic saline, which was not allowed. The primary efficacy outcome was absolute change from baseline in per cent predicted FEV_1, in the three studies.

The studies were generally well conducted with no major methodological issues identified. The studies were appropriately blinded with allocation concealment by interactive voice/web response system. There were few dropouts. KONNECTION being a crossover study, patients served as their own controls. Baseline characteristics were generally similar across treatment groups in STRIVE and ENVISION. The clinical expert consulted on this review confirmed that the efficacy outcomes included in the studies and the CADTH Common Drug Review (CDR) systematic review are clinically relevant. The use of a placebo comparator was considered appropriate, given the first-in-class therapy status of ivacaftor. Studies were not of sufficient size or duration to examine survival as an end point.

Generalizability of the findings is limited to patients with mild to moderate severity CF who are at least six years old. It is unknown to what extent these findings apply to younger patients or to those with more severe disease. Of note, although the inclusion criteria extended to the elderly (≥ 65 years), there were no patients actually recruited in the ≥ 65 years age group, hence the applicability of the findings in this age group is uncertain. Patients with severe renal and hepatic disease were excluded from the studies; hence, the applicability of the findings to these patient groups is uncertain.

Efficacy

No deaths were reported in any of the three studies. Compared with placebo, ivacaftor-treated patients experienced statistically significant improvements in per cent predicted FEV_1 of ≥ 10% in KONNECTION through eight weeks and in both STRIVE and ENVISION through 24 weeks and 48 weeks. While no published information on the minimal clinically important difference in FEV_1 in CF was identified by CDR, the clinical expert consulted for this review indicated that a change of this magnitude is considered clinically meaningful and that improvement in FEV_1 leads to better survivorship. The between-treatment differences were also statistically significant for subgroups based on FEV_1 status and age in KONNECTION through eight weeks, excepting for the age group 6 to 11 years. The between-treatment differences were also statistically significant for subgroups based on FEV_1 status and age in STRIVE through 24 weeks and 48 weeks. The between-treatment differences for subgroups based on FEV_1 status were not reported or not statistically significant in ENVISION.

Further, between-treatment differences in patient-reported respiratory symptoms favouring ivacaftor over placebo are supportive of FEV_1 findings. The statistically significant improvements in patient-reported respiratory symptoms achieved with ivacaftor, as measured by the Cystic Fibrosis Questionnaire-Revised (CFQ-R) in KONNECTION and STRIVE, exceed the minimal clinically important difference. Finally, ivacaftor produced statistically significantly greater gains in body weight and body mass index (BMI)-for-age z-scores and greater decreases in sweat chloride, compared with placebo in the three trials.

Two open-label extension studies (KONNECTION part 2 enrolling patients who completed part 1 of KONNECTION, and PERSIST enrolling patients who completed either STRIVE or ENVISION) were conducted. Overall, the efficacy results through 24 weeks in KONNECTION part 2 were consistent with those observed over eight weeks of treatment in KONNECTION. Sustained improvements in FEV_1 per cent predicted, CFQ-R respiratory domain, and body weight among patients treated with ivacaftor in STRIVE and ENVISION were sustained during PERSIST.

Harms

Safety information was reported over a treatment period of eight weeks in KONNECTION and over 48 weeks in STRIVE and ENVISION. There were no deaths reported in any of the three included studies. Serious adverse events (SAEs) were numerically less frequent for ivacaftor compared with placebo, with CF lung exacerbations representing the most commonly encountered SAE in the studies. Withdrawal due to adverse event (WDAE) was infrequent in the included studies, with one ivacaftor-treated patient withdrawing due to an adverse event in the STRIVE study only. Adverse effects commonly seen with ivacaftor were adverse effects of upper respiratory tract infection, headache, dizziness, and rash. In the three studies, numbers of adverse events that could signal possible hepatic harms were small in number overall, with no clear pattern emerging between groups. Hepatic adverse events such as increased alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transpeptidase (GGT), and hepatic enzymes were examined. In KONNECTION part 2, an open-label extension study of KONNECTION part 1, no new safety concerns were identified. The overall safety profile observed during PERSIST, an open-label extension study, was generally consistent with that seen during STRIVE and ENVISION.

Other Considerations

Ivacaftor was studied in patients homozygous for the more common, F508del-CFTR mutation in a 16-week randomized, double-blind, placebo-controlled parallel-group trial, but was not found to be effective in this CF population.

Planned, ongoing or recently completed studies are likely to provide further insights into efficacy and safety of ivacaftor treatment in CF patients. Six such studies[6-11] enrolling CF patients with a gating mutation were identified. One study[8] is open but not recruiting patients, four studies[6,9-11] are recruiting patients, and one study[7] is completed but at this time results are not yet available. Of these six studies, two studies[7,9] are specifically on CF patients younger than six years of age, a patient group for whom currently information regarding effect of ivacaftor treatment is lacking. Of these two studies, one study[7] is an open-label study evaluating the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in children with CF who are two through five years of age and have a CFTR gating mutation in at least one allele; the other study[9] is an open-label study on CF patients younger than six years of age with a CFTR gating mutation in at least one allele and its goal is to evaluate the long-term safety and pharmacodynamics of ivacaftor treatment and to explore efficacy of long-term ivacaftor treatment.

The Food and Drug Administration has not approved ivacaftor treatment for CF patients with a G970R mutation.

Pharmacoeconomic Summary

Summary of Economic Analysis

The manufacturer submitted a cost-utility analysis (CUA) from a Canadian health care payer's perspective.[12] The economic evaluation compared ivacaftor plus standard of care (SoC) with SoC alone — where SoC could consist of, but not limited to, respiratory, nutritional, and rehabilitative support such as mucolytic drugs, osmotic drugs, antibiotics, bronchodilators, pancreatic enzymes, dietetic therapy, and chest physiotherapy over the lifetime of CF patients (80 years). The model was based on a patient-level simulation to estimate clinical outcomes and costs associated with CF treatment. The model included five health states: normal lung function ($FEV_1 \geq 90\%$), mild (FEV_1 70% to 90% predicted), moderate (FEV_1 40% to 70% predicted), severe ($FEV_1 < 40\%$ predicted), and death. Transition between health states was based on CF survival prediction equations. The model used patient-level data from clinical trials (KONNECTION, STRIVE, ENVISION, and PERSIST). In the base case, the manufacturer assumed that ivacaftor would cause a persistent improvement of lung function, while

patients on SoC alone would have a continuous annual decline in lung function. The manufacturer also assumed that the cost of ivacaftor would be reduced by 82% after 12.5 years (patent expiry). Costs and quality-adjusted life years (QALYs) for each individual patient were estimated based on assumptions relating to the relationship with FEV_1 per cent predicted. Thus, the model predicted total cost, QALYs and survival for each patient both with ivacaftor and without ivacaftor.

The model was a direct modification of the original ivacaftor cost-effectiveness analysis submitted to CDR, with a few updates, such as:
- Baseline characteristics of 39 patients with non-G551D mutations included in KONNECTION were added to the model, leading to a total sample size of 252 individuals (G551D and non-G551D mutations).
- Utility values were obtained from a survey completed by seven directors of CF centres in Australia, while the previous submission used trial-based utility estimates.
- Mean values of forced expiratory volume in one second (FEV_1) were used instead of the median values used in the previous submission.
- Long-term data from the PERSIST extension study were used to support sustained efficacy of ivacaftor up to 144 weeks.
- The manufacturer assumed that patients consume ▇▇ of the full dose of ivacaftor on an annual basis (to account for adherence and pharmacokinetic dose adjustments).

Results of Manufacturer's Analysis
The base case results showed that the incremental cost-effectiveness ratio for ivacaftor plus SoC compared with SoC alone was $356,349 per QALY and $444,746 per life year gained.

Interpretations and Key Limitations
CDR identified several limitations with the submitted analysis. CDR analysis assumed the following:
- Trial-based utility would provide more accurate estimates than those used by the manufacturer, which came from a very small sample size (N = 7).
- No price reduction after patent expiry.
- CF costs are not a function of FEV_1.
- Patients consume 93% of the full dose of ivacaftor on an annual basis (based on Canadian data presented in the manufacturer's submission) instead of ▇, as assumed in the manufacturer's base case.

When considering more conservative input estimates and assumptions, CDR noted that the incremental cost-utility ratio (ICUR) for ivacaftor plus SoC compared with SoC alone was $850,932 per QALY and the incremental cost-effectiveness ratio (ICER) was $844,236 per life year.

Conclusions
Compared with placebo, ivacaftor showed a consistent, statistically significant, and clinically meaningful improvement in per cent predicted FEV_1 from baseline through eight weeks for KONNECTION and through 24 weeks and 48 weeks for STRIVE and ENVISION across the spectrum of pediatric and adult populations studied. The magnitude of effect observed (~ 10%) was achieved when ivacaftor was used as an add-on therapy to a stable regimen of CF therapies. In addition, ivacaftor treatment demonstrated statistically significant and clinically meaningful improvements in patient-reported respiratory symptoms as measured by the CFQ-R in KONNECTION and STRIVE. Compared with placebo a statistically significant greater weight gain was observed with ivacaftor in all three studies. There were no significant

differences between ivacaftor and placebo with respect to pulmonary exacerbation requiring hospitalization.

Ivacaftor treatment resulted in few WDAEs and SAEs. Nonetheless, baseline and periodic monitoring of liver transaminases are recommended by the US Food and Drug Administration (FDA) and Health Canada, given this population's underlying risk for elevations in liver enzymes. Comparative information beyond 48 weeks is lacking but open-label extension studies suggest sustained efficacy based on per cent predicted FEV_1, CFQ-R (respiratory domain), weight, and BMI. Also, no additional safety signals were identified.

Findings from these studies are applicable to patients aged six years or older with mild to moderate CF (FEV_1 > 40% predicted) and having a G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R mutation on at least one allele. There is no available randomized controlled trial (RCT) evidence regarding the efficacy of ivacaftor in patients having a CFTR mutation who are less than six years of age, or who have more severe disease (FEV_1 < 40% predicted).

TABLE 1: SUMMARY OF RESULTS

Outcome	KONNECTION (Study 111)		STRIVE (Study 102)		ENVISION (Study 103)	
	IVA	PL	IVA	PL	IVA	PL
Mortality						
n (%)	0	0	0	0	0	0
Per cent predicted FEV_1						
N	38	37	83	78	26	25
Baseline, mean	76.37	79.34	63.46	63.67	84.73	83.01
Change from baseline LS mean	7.49	−3.19	10.13	−0.37	10.67	0.68
Mean difference (95% CI) *P* value versus PL	10.67 (7.26 to 14.10) < 0.0001		10.50 (8.50 to 12.50) < 0.0001		9.99 (4.52 to 15.46) 0.0006	
Exacerbation						
Number of events (event rate)	10 (0.159)	10 (0.197)	47 (0.59)	99 (1.38)	8	4
Rate ratio (95% CI) *P* value versus PL	0.81 (0.39 to 1.69) 0.5687		0.43 (0.27 to 0.68) 0.0003		NR 0.4986	
CFQ-R (respiratory)[a]						
N	38	37	80	70	26	25
Baseline, mean	70.61	74.55	NR	NR	78.20	80.13
Change from baseline LS mean	8.96	−0.68	5.94	−2.65	3.69	−1.19
Mean difference (95% CI) *P* value versus PL	9.63 (4.53 to 14.73) 0.0004		8.60 (5.32 to 11.87) < 0.0001		4.88 (−0.44 to 10.20) 0.0713	
SAEs						
n (%)	4 (10.5)	8 (21.6)	20 (24.10)	33 (42.3)	5 (19.2)	6 (23.1)
WDAEs						
n (%)	0	0	1 (1.2)	4 (5.1)	0	1 (3.8)

CI = confidence interval; CFQ-R = Cystic Fibrosis Questionnaire-Revised; FEV_1 = forced expiratory volume in one second; IVA = ivacaftor; LS = least square; n = number of patients with event; N = number of patients; NR = not reported; PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Data for patient response.
Note: Results presented are those for treatment duration of 8 weeks for KONNECTION and 48 weeks for STRIVE and ENVISION.
Source: KONNECTION Clinical Study Report,[13] STRIVE Clinical Study Report,[14] ENVISION Clinical Study Report.[15]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Cystic fibrosis (CF), an autosomal recessive condition,[1] is the most common fatal genetic disease affecting children and young adults in Canada.[2] It is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, located on chromosome seven. There have been approximately 1,900 CFTR variants that have been identified among CF patients.[16] The CFTR variants have been classified as: impaired biosynthesis (class I); defective protein maturation and accelerated degradation (class II); defective regulation of CFTR at the plasma membrane (class III); defective chloride conductance (class IV); diminished CFTR transcription (class V); and accelerated turnover at the cell surface (class VI).[17] CFTR variants within classes I to III are associated with severe CF as they are considered non-functional, while CFTR variants in classes IV to VI may retain CFTR function.[17] The G551D-CFTR class III gating mutation is the third most common CFTR variant, as it is prevalent in 4.4% of CF patients,[17] while approximately 1% of CF patients have other class III gating mutations such as G178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P, and G1349D.[16]

This CFTR gene encodes for a chloride channel that regulates transport of salt and water across cell membranes. When CFTR is dysfunctional, secretions become tenacious and sticky, resulting in pathology in multiple organ systems, most notably the lungs and gastrointestinal tract. In the lungs, this results in airway obstruction, chronic endobronchial infection and inflammation, which ultimately leads to destruction of lung tissue with development of bronchiectasis and loss of lung function.[18] Lung disease accounts for 85% of mortality.[18] Chronic endobronchial infection of the airways with bacterial pathogens, such as Pseudomonas aeruginosa, which occurs in almost half of individuals with CF by 18 years of age,[3] is associated with a more rapid loss of lung function.[19] 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 survivorship.[20] 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. Maintenance of adequate nutrition is paramount, since this is associated with improved clinical outcome and longevity.[21]

While there is no cure for the underlying disease process, current therapies have resulted in increased longevity for CF patients. Currently, the number of adults with CF exceeds that of children.[3] Median life expectancy has reached 48 years, based on recent Canadian statistics.[3]

To date, no therapies have addressed the underlying genetic defect or corrected the abnormal functioning of the CFTR gene. In this way, ivacaftor is a novel therapy that addresses the fundamental origin of the disease process and that may have disease-modifying potential.

1.2 Standards of Therapy

The goals of CF therapy until now have been the 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 drugs that are antibiotics, anti-inflammatory

drugs or mucolytic drugs. Nutritional treatments consist of high-calorie and high-fat diets[4] and for those with pancreatic insufficiency, pancreatic enzyme replacement.

1.2.1 Physiotherapy

Physiotherapy, the mainstay of CF pulmonary management, is often started in infants as percussion, or "clapping," followed by postural drainage. Positive end-expiratory pressure (PEP) is the best studied and most commonly used physiotherapy technique in CF.[22]

1.2.2 Antibiotics

Antibiotics are prescribed both to treat acute pulmonary exacerbations and as chronic, suppressive therapy to reduce the burden of lung pathogens, especially *Pseudomonas aeruginosa*.[23] Patients are usually treated with a course of oral or intravenous antibiotics for a period of one to three weeks for acute exacerbations while inhaled antibiotics are used for chronic suppressive therapy to decrease bacterial load and inflammation.

Inhaled tobramycin has been traditionally prescribed as a lifelong, chronic suppressive treatment, most often used for one-month periods in alternate months.[24] Although systemic toxicities are relatively rare with inhaled tobramycin, ototoxicity and nephrotoxicity have been reported, particularly when administered along with intravenous or oral aminoglycosides.[25-27] Moreover, inhaled (nebulized) tobramycin is a time-consuming treatment, which requires 15 to 20 minutes twice daily for its administration;[28,29] by comparison, a dry-powder inhalation has also recently become available, but is not yet in widespread use.[30] Aztreonam and colistin are other inhaled (nebulized) antibiotic treatment options used in cases of antimicrobial resistance or tobramycin treatment failure.[31-33]

1.2.3 Anti-inflammatory Drugs

Several anti-inflammatory treatments have been used as adjunctive therapies in CF to diminish inflammation in the airways.[34,35] Azithromycin, an antibiotic with anti-inflammatory properties, is most commonly used. Treatment guidelines recommend using azithromycin in CF patients aged six years and older with chronic *Pseudomonas aeruginosa* persistently present in cultures of the airways.[18]

1.2.4 Mucolytic Drugs

Mucolytic drugs may also be used as adjunctive therapy. Dornase alfa is recommended for use in patients aged six years and older with moderate to severe lung disease to breakdown excess free DNA in mucous secretions, thereby enhancing airway clearance and lowering the frequency of acute exacerbations.[18] Nebulized hypertonic saline is an inexpensive alternative that enhances mucociliary clearance through hydration of airway surface liquid; however, its strong salty taste may limit its use. Moreover, it can induce bronchospasm and requires twice daily administration over 15 to 20 minutes per session. Though not FDA-approved for CF,[36] it is nonetheless recommended as an option for improving lung function in patients aged six years and older.[18]

1.2.5 Nutritional Support

Nutritional support is an integral component of CF treatment.[37] There is good evidence from population-based studies that normal ranges of weight-for-age, height-for-age, and weight-for-height percentiles are associated with better pulmonary function (per cent predicted FEV_1) and survival for adults and children with CF.[20,38] Those with ideal body weight greater than 85% have better prognosis at five years.[39] This may be achieved with high-calorie and high-fat diets[4] and for those with pancreatic insufficiency, pancreatic enzyme replacement before meals to assist with absorption of fat and nutrients.

1.2.6   Neonatal Screening

Neonatal screening for CF has begun in the last few years in most provinces in Canada. This allows individuals affected with CF to be identified and started on aggressive treatments early in life, which is linked to better outcome.[40] Genotyping for mutations in the CFTR gene is routinely performed on almost all CF patients in Canada and is part of the newborn screening process.

1.3   Drug

Ivacaftor has a Health Canada indication for the treatment of CF in patients age six years and older who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R. The Health Canada recommended dose, for children six years of age and older, is 150 mg every 12 hours with fat-containing food. Ivacaftor is available as 150 mg oral tablets.

A first-in-class CFTR potentiator, ivacaftor works by prolonging the time that activated CFTR channels remain open, thereby enhancing the regulation of chloride and water transport across cell membranes.[5] This results in improved functioning of multiple organs, most notably lungs and gastrointestinal tract.

Indication under review
Kalydeco is indicated for treatment of cystic fibrosis (CF) in patients age six years and older who have one of the following mutations in the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R.
Listing criteria requested by sponsor
As per indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of ivacaftor 150 mg in CF patients of age six years and older who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R.

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies in support of the Health Canada indication provided in the manufacturer's submission to the CADTH Common Drug Review (CDR) as well as those meeting the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients ≥ 6 years of age with cystic fibrosis who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R. Subgroups: • Severity of disease (based on baseline FEV_1) • Age
Intervention	Ivacaftor, 1 tablet (150 mg) taken orally every 12 hours
Comparators	• Standard of care (may include antibiotics, anti-inflammatory drugs, mucolytic drugs, pancreatic enzymes and physiotherapy) • Placebo
Outcomes	**Key efficacy outcomes:** • Mortality/survival • Disease progression (based on FEV_1) • Acute pulmonary exacerbations or infection • Health-related quality of life by validated measures **Other efficacy outcomes:** • Hospitalization • Weight/BMI • Changes in concomitant CF medication • Sweat chloride levels **Harms outcomes:** AEs, SAEs, WDAEs Notable harms: hepatic AE
Study Design	Published and unpublished RCTs (excluding studies phase 2 and below, if not considered pivotal)

AE = adverse event; BMI = body mass index; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; FEV_1 = forced expiratory volume in one second; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH), and keywords. The main search concepts were Kalydeco (ivacaftor) and Cystic Fibrosis.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on July 14, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on November 19, 2014. 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 (www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), and Internet Search. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

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

3. RESULTS

3.1 Findings From the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 3 and described in Section 3.2. A list of excluded studies is presented Appendix 3: Excluded Studies.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

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                    ┌─────────────────────────┐
                    │          128            │
                    │ Citations identified in │
                    │  literature search      │
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│ Potentially relevant    │   │ Potentially relevant    │
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        │                12                   │
        │        Reports included             │
        │ Presenting data from 3 unique       │
        │ studies                             │
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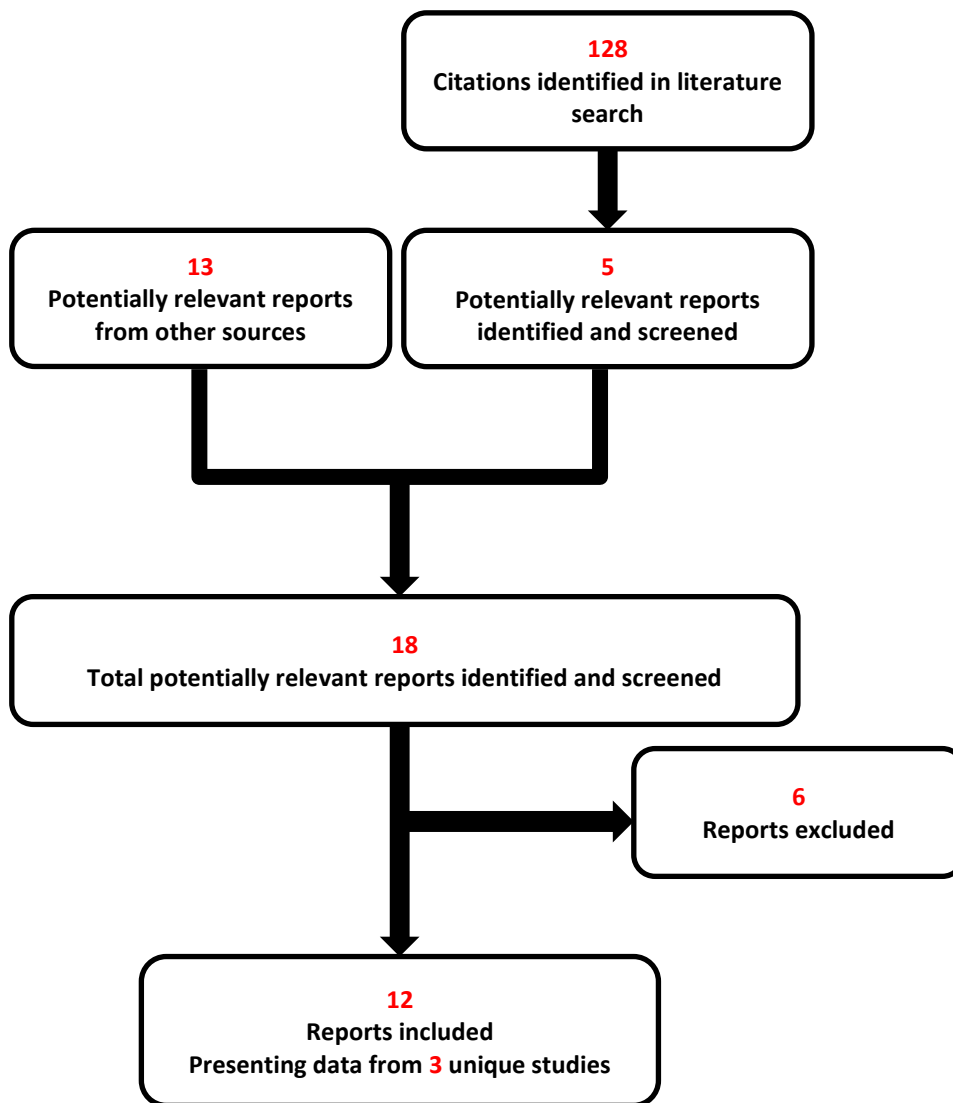
TABLE 3: DETAILS OF INCLUDED PHASE 3 STUDIES

		KONNECTION	STRIVE	ENVISION[a]
DESIGNS AND POPULATIONS	**Study Design**	Multi-centre DB RCT, placebo-controlled, crossover study Stratified by age (6 to 11 years, 12 to 17 years, ≥ 18 years) and % predicted FEV$_1$ (< 70%, 70% to 90%, > 90%)	Multi-centre, DB, placebo-controlled, parallel-group RCT Stratified by age (< 18 years, ≥ 18 years) and % predicted FEV$_1$ (< 70, ≥ 70)	Multi-centre, DB, placebo-controlled, parallel-group RCT Stratified by % predicted FEV$_1$ (< 70%, 70% to 90%, > 90%)
	Locations	North America and Europe	Canada, USA, Europe, Australia	Canada, USA, Europe, Australia
	Randomized (N)	39	167	52
	Inclusion Criteria	• 6 years of age or older • Minimum weight of 15 kg at screening • Sweat chloride value ≥ 60 mmol/L **or** 2 CF-causing mutations **and** chronic sinopulmonary disease and at least 1 allele with CFTR gating mutations: G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D • FEV$_1$ ≥ 40% predicted normal	• 12 years of age or older • Sweat chloride value ≥ 60 mmol/L **or** 2 CF-causing mutations **and** chronic sinopulmonary disease **or** GI/nutritional abnormalities • G551D-CFTR mutation in at least 1 allele • FEV$_1$ 40% to 90% (inclusive) of predicted normal	• 6 to 11 years of age • Weight > 15 kg • Sweat chloride value ≥ 60 mmol/L **or** 2 CF-causing mutations **and** chronic sinopulmonary disease **or** GI/nutritional abnormalities • G551D-CFTR mutation in at least 1 allele • FEV$_1$ 40% to 105% (inclusive) of predicted normal
	Exclusion Criteria	• G551D mutation on at least 1 allele • Acute URTI or LRTI within 4 weeks before Day 1 • Evidence of cataract or lens opacity at screening • Hgb < 10 g/dL at screening • Abnormal liver function (LFTs > 3× ULN) • Abnormal renal function • Transplant history • Colonization with *Burkholderia cenocepacia*, *B. dolosa,* or *Mycobacterium abscessus* • Use of inhaled hypertonic saline treatment or inhibitors/inducers of CYP3A4 • Pregnant, breastfeeding, or not willing to follow contraception requirements	• Acute URTI or LRTI, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks of randomization • Hgb < 10 g/dL • Abnormal liver function (LFTs > 3× ULN) • Abnormal renal function (CrCL < 50 mL/min) • Transplant history • Colonization with *B. cenocepacia*, *B. dolosa,* or *M. abscessus* • Use of inhaled hypertonic saline or inhibitors/inducers of CYP3A4 • Pregnant, breastfeeding, or not willing to follow contraception requirements	• Acute URTI or LRTI, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks prior to randomization • Hgb < 10 g/dL • Abnormal liver function (LFTs > 3× ULN) • Abnormal renal function (CrCL < 89 mL/min/1.73 m2) • Transplant history • Colonization with *B. cenocepacia*, *B. dolosa,* or *M. abscessus* • Use of inhaled hypertonic saline or inhibitors/inducers of CYP3A4

		KONNECTION	STRIVE	ENVISION[a]
DRUGS	**Intervention**	Ivacaftor, 1 tablet (150 mg) taken orally every 12 hours Patients were to remain on stable regimen of CF drugs	Ivacaftor, 1 tablet (150 mg) taken orally every 12 hours Patients were to remain on stable regimen of CF drugs	Ivacaftor, 1 tablet (150 mg) taken orally every 12 hours Patients were to remain on stable regimen of CF drugs
	Comparator(s)	Matching placebo Patients were to remain on stable regimen of CF drugs	Matching placebo Patients were to remain on stable regimen of CF drugs	Matching placebo Patients were to remain on stable regimen of CF drugs
DURATION	**Phase**			
	Run-in[b]	2 weeks	2 weeks	2 weeks
	Double-blind	20 weeks to 24 weeks	48 weeks[c]	48 weeks[c]
	Follow-up[d]	Opportunity to continue on to open-label extension study	Opportunity to continue on to open-label extension study	Opportunity to continue on to open-label extension study
OUTCOMES	**Primary End Point**	Absolute change from baseline in per cent predicted FEV_1 through week 8 in each period of part 1	Absolute change from baseline in per cent predicted FEV_1 through week 24	Absolute change from baseline in per cent predicted FEV_1 through week 24
	Other End Points	Secondary end points: Absolute changes from baseline in CFQ-R respiratory domain score, sweat chloride BMI and BMI-for-age z-score Tertiary end points: Pulmonary exacerbation, changes from baseline in CFQ-R non-respiratory domain scores	Secondary end points: Absolute changes from baseline in CFQ-R respiratory domain score, sweat chloride, and weight, through weeks 24 and 48 Tertiary end points: Pulmonary exacerbation, change from baseline in EQ-5D score	Secondary end points: Absolute changes from baseline in CFQ-R respiratory domain score, sweat chloride and weight, through weeks 24 and 48 Tertiary end points: Pulmonary exacerbation
NOTES	**Publications**	None	Ramsey et al.[41]	Davies et al.[42]

BMI = body mass index, CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane regulator; CFQ-R = Cystic Fibrosis Questionnaire-Revised; CrCL = creatinine clearance; CYP3A4 = cytochrome P450 3A4; DB = double-blind; EQ-5D = EuroQol Questionnaire; FEV_1 = forced expiratory volume in one second; GI = gastrointestinal; Hgb = hemoglobin; LFT = liver function test; LRTI = lower respiratory tract infection; RCT = randomized controlled trial; ULN = upper limit of normal; URTI = upper respiratory tract infection.

Note: 10 additional reports were included: Clinical Study Reports,[13-15,43-45] Submission binder,[16] Health Canada report,[46] and FDA reports.[36,47]

[a] Patients in ENVISION may have participated in an initial single-dose, open-label pharmacokinetic study (part A) before proceeding to the RCT (part B).

[b] Run-in was stated as being used to ensure that baseline assessments performed on Day 1 of randomization were reflective of patients' adherence to usual CF medication regimens.

[c] STRIVE and ENVISION were originally designed to be carried out over 24 weeks, but the duration was extended to 48 weeks following a pre-application meeting with the FDA.[36] Therefore, the total duration of blinded treatment in both trials was 48 weeks, not 24 weeks.

[d] In KONNECTION patients were offered the opportunity to participate in an open-label, unblinded extension study (part 2 of the study). In STRIVE and ENVISION, upon completion of 48 weeks of blinded therapy, patients were offered the opportunity to participate in an open-label, unblinded extension study (Study 105).

Source: Clinical Study Report-KONNECTION,[13] Clinical Study Report-STRIVE,[14] and Clinical Study Report-ENVISION.[15]

3.2   Included Studies
3.2.1   Description of Studies
Three multi-national, multi-centre, randomized, placebo-controlled, double-blind, phase 3 studies (KONNECTION,[13] STRIVE,[14] and ENVISION[15]) met the inclusion criteria for this systematic review. The studies compared the efficacy and safety of ivacaftor versus placebo in patients with CF. All three studies included ≥ 50% of patients from North America.

KONNECTION was a crossover study with an initial treatment duration of eight weeks followed by a washout period of four to eight weeks and subsequent treatment crossover for an additional eight weeks, for a total study duration of 20 weeks to 24 weeks. The initial treatment period is referred to as period 1 and the treatment period after crossover is referred to as period 2. STRIVE and ENVISION both were parallel group studies with treatment duration of 24 weeks which was later extended to 48 weeks, during which double blinding was still maintained.

3.2.2   Populations
a)   Inclusion and Exclusion Criteria
KONNECTION included CF patients of age six years or older and with at least one allele with a non-G551D gating mutation: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R. Both STRIVE and ENVISION included CF patients with at least one allele with a G551D gating mutation. STRIVE included patients of age 12 years and older and ENVISION included patients of age 6 to 11 years. All three studies included patients with per cent predicted FEV_1 no less than 40%.

All three studies excluded patients with abnormal liver function or abnormal renal function or patients using inhaled hypertonic saline.

b)   Baseline Characteristics
Both KONNECTION and STRIVE included pediatric and adult patients and the mean age was 23 years in KONNECTION and 25 years in STRIVE. ENVISION included pediatric patients of mean age 9 years. In all three studies the majority of patients were Caucasian; however, there was greater ethnic diversity in KONNECTION. The proportions of Caucasians were 74% in KONNECTION, 87% in ENVISION and 98% in STRIVE. The mean per cent predicted FEV_1 of patients ranged between 64% and 84%. As determined by FEV_1 status, lung function was better in patients in ENVISION, which exclusively enrolled pediatric patients, compared with KONNECTION and STRIVE, which enrolled both pediatric and adult patients. The mean BMI of patients enrolled in KONNECTION and STRIVE was similar (BMI = 22) and mean BMI was 17 for patients in ENVISION. Sweat chloride levels ranged between 98 mmol/L and 105 mmol/L, being highest in patients in ENVISION and lowest in patients in KONNECTION.

Baseline characteristics were generally similar between groups within the three trials with only a few imbalances noted. In ENVISION, compared with the placebo group, the ivacaftor group had a lower proportion of males (34.6% versus 61.5%) and lower proportion of patients with per cent predicted FEV_1 < 70% (15.4% versus 30.8%). The overall baseline mean FEV_1 was similar in the ivacaftor and placebo groups, at 84.7% and 83.7% respectively.

There were some between-group differences in prior medication use. In STRIVE, compared with placebo group, the ivacaftor group had fewer patients with prior use of the following medications: dornase alfa (65.1% versus 73.1%), salbutamol (   ), tobramycin (33.7% versus 44.9%), and seretide (   ). In ENVISION, compared with placebo group, the ivacaftor group had fewer patients with prior use of dornase alfa (69.2% versus 84.6%). Most patients in KONNECTION, STRIVE, and

ENVISION had comorbid pancreatic insufficiency, with slightly more patients in the placebo group (96.2%) of STRIVE presenting with this comorbidity than in the ivacaftor group (89.2%). Sinus disease and gastroesophageal reflux disease (GERD) were also prevalent in all three studies, with sinus disease presenting slightly more commonly in the ivacaftor group (56.6%) than placebo (44.9%) in the STRIVE study. In STRIVE, there were fewer patients with asthma in the ivacaftor group compared with the placebo group (21.7% versus 33.3%).

Details of baseline characteristics are presented in Table 4.

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS OF PATIENTS IN PHASE 3 STUDIES

Characteristic	KONNECTION (Study 111, part 1)		STRIVE (Study 102)		ENVISION (Study 103, part B)	
	T1 (IVA-PL) (N = 20)	Tx2 (PL-IVA) (N = 19)	IVA (N = 83)	PL (N = 78)	IVA (N = 26)	PL (N = 26)
Age (years)						
Mean ± SD	23.8 ± 13.25	21.7 ± 12.92	26.2 + 9.85	24.7 + 9.21	8.9 ± 2.0	8.9 ± 1.9
Median	24.0	15.0	25.0	23.0	9.0	8.5
Range	6 to 57	6 to 47	12 to 53	12 to 53	6 to 12	6 to 12
< 18 years, N (%)	9 (45)	10 (52.6)	19 (22.9)	17 (21.8)	26 (100)	26 (100)
Sex, N (%)						
Male	13 (65.0)	9 (47.4)	39 (47.0)	38 (48.7)	9 (34.6)	16 (61.5)
Race, N (%)						
White	15 (75.0)	14 (73.7)	81 (97.6)	77 (98.7)	22 (84.6)	23 (88.5)
Height (cm)						
Mean ± SD	161.30 ± 19.64	153.84 ± 20.91	167.7 ± 10.0	166.5 ± 10.3	134.9 ± 14.4	132.6 ±12.2
Weight (kg)						
Mean ± SD	59.80 ± 18.66	55.01 ± 25.76	61.7 ± 14.3	61.2 ± 13.9	31.8 ± 9.9	30.0 ± 7.2
Weight-for-age z-score (points)						
Mean ± SD	0.38 ± 1.18 (N = 9)	−0.18 ± 1.03 (N = 10)	−0.46 ± 1.0 (n = 24)	−0.57 ± 0.9 (n = 23)	−0.02 ± 1.0	−0.16 ± 0.77
BMI						
Mean ± SD	22.26 ± 4.12	21.99 ± 5.88	21.7 ± 3.7	21.9 ± 3.5	17.1 ± 2.6	16.8 ± 1.7
BMI-for-age z-score (points)						
Mean ± SD	0.50 ± 1.16 (n = 9)	0.23 ± 1.09 (n = 10)	−0.47 ± 0.92 (n = 24)	−0.56 ± 0.78 (n = 23)	0.09 ± 0.92	0.08 ± 0.81
Per cent predicted FEV$_1$						
Mean ± SD	77.74 ± 21.57	79.05 ± 20.90	63.5 ± 16.1	63.7 ± 16.8	84.7 ± 15.8	83.7 ± 20.4
Median	80.38	85.60	66.1	67.2	85.2	85.4
Range	42.90 to 118.72	42.97 to 104.07	37.3 to 98.2	31.6 to 97.1	52.4 to 133.8	44.0 to 116.3
< 70%, N (%)	7 (35.0)	6 (31.6)	49 (59.0)	45 (57.7)	4 (15.4)	8 (30.8)
≥ 70%, N (%)	13 (65.0)	13 (68.4)	34 (41.0)	33 (42.3)	22 (84.7)	18 (69.3)
CFQ-R Respiratory domain						
Mean ± SD	NR	NR	70.2 ± 16.4	69.0 ± 19.2	78.2 ± 18.3	80.1 ± 17.8

Characteristic	KONNECTION (Study 111, part 1)		STRIVE (Study 102)		ENVISION (Study 103, part B)	
	T1 (IVA-PL) (N = 20)	Tx2 (PL-IVA) (N = 19)	IVA (N = 83)	PL (N = 78)	IVA (N = 26)	PL (N = 26)
EQ-5D index score						
Mean ± SD	NR	NR	0.93 ± 0.09	0.94 ± 0.11	NR	NR
Sweat chloride (mmol/L)						
Mean ± SD	94.58 ± 22.74	100.66 ± 12.76	100.4 ± 10.0	100.1 ± 10.6	104.3 ± 14.5	104.8 ± 8.9
Prior medication[a] (> 30% use), N (%)						
Pancrelipase	▮	▮	█	█	█	█
Pancreatin	█	█	NR	NR	NR	NR
Dornase alfa	█	█	54 (65.1)	57 (73.1)	█	█
Azithromycin	█	█	51 (61.4)	50 (64.1)	█	█
Salbutamol	█	█	█	█	█	█
Tobramycin	▮	▮	28 (33.7)	35 (44.9)	▮	▮
Seretide	█	█	█	█	▮	▮
CF-related comorbid conditions (≥ 20%)						
Pancreatic insufficiency	█	█	█	█	█	█
Sinus disease (symptomatic)	█	█	█	█	█	█
GERD	█	█	█	█	█	█
Asthma	█	█	█	█		
CF-related diabetes	NR	NR	█	█		
Number of hospitalizations in past year						
Unplanned (mean ± SD)	█	█	█	█	█	█

BMI = body mass index; FEV$_1$ = forced expiratory volume in one second; IVA = ivacaftor; NR = not reported; PL = placebo; SD = standard deviation; Tx1 = treatment sequence 1 = ivacaftor→ washout→ placebo; Tx2 = treatment sequence 2 = placebo→ washout→ ivacaftor.
[a] If ≤ 30% use of prior mediction then data not reported here and indicated by –.
Source: Clinical Study Report-KONNECTION,[13] Clinical Study Report-STRIVE,[14] and Clinical Study Report-ENVISION.[15]

3.2.3 Interventions

Patients received either ivacaftor (150 mg oral tablets) or matching placebo every 12 hours. Both were blue film-coated tablets with wax. During the study it was recommended that patients remain on stable medication regimens for their CF, with the exception of inhaled hypertonic saline. Details of concomitant medications used by greater than 15% of patients in KONNECTION, STRIVE and ENVISION are shown in Appendix 4: Detailed Outcome Data in Table 7, Table 8, and Table 29 respectively.

In KONNECTION, patients were randomly assigned to one of two treatment sequences: ivacaftor for eight weeks, washout period of four to eight weeks followed by placebo for eight weeks, or placebo for eight weeks, washout period of four to eight weeks followed by ivacaftor for eight weeks. For patients who were not on cycling antibiotics, the washout period was four weeks. For patients who were on a stable regimen of inhaled cycling antibiotics, the washout period was extended to approximately eight

weeks so that the week 12 visit was timed to occur at the end of an off-cycle but no less than 14 days after the last dose of inhaled antibiotics in the previous on-cycle.

In STRIVE and ENVISION, patients were randomly assigned to either ivacaftor or placebo treatments for 24 weeks. Later it was decided to extend the treatment period to 48 weeks, maintaining double blinding.

3.2.4 Outcomes

The primary efficacy outcome was the absolute change from baseline in per cent predicted FEV_1 over eight weeks for KONNECTION and over 24 weeks for STRIVE and ENVISION. In addition, the absolute change from baseline in per cent predicted FEV_1 over 48 weeks was a secondary outcome in STRIVE and ENVISION.

In KONNECTION, STRIVE, and ENVISION other secondary efficacy outcomes included BMI (kg/mm^2), BMI-for-age z-score, sweat chloride, and respiratory domain of CFQ-R. Weight was included as a secondary outcome in STRIVE and ENVISION and included as additional outcome in KONNECTION. In all these three phase 3 studies non-respiratory domains of CFQ-R, pulmonary exacerbations, and hospitalization were considered as additional outcomes.

Per cent predicted FEV_1 is an established end point for assessing changes in pulmonary function in both clinical trials and clinical practice. However, there are no published data on the clinically meaningful magnitude of change of FEV_1 in CF.[48] According to the clinical expert consulted for this review, a change in per cent predicted FEV_1 would be considered reasonable if 5% and substantial if 10%.

The CFQ-R questionnaire is a health-related quality of life instrument specific for CF, comprised of three modules and nine domains (including a respiratory domain), that measures quality of life, health perception, and symptoms over a two-week recall period.[36] The respiratory domain was the primary analytic focus of the CFQ-R data insomuch as it was identified as a key secondary end point in the included studies. The minimal clinically important difference (MCID) for the respiratory domain of the CFQ-R is considered to be four points for patients with stable disease and 8.5 points for patients with exacerbation.[49]

EQ-5D[50,51] is a generic quality of life (QoL) instrument that has been applied to a wide range of health conditions and treatments including CF. It consists of 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. Assessment of QoL using EQ-5D was performed only in STRIVE. The MCID for the EQ-5D ranges from 0.033 to 0.074.[52] The validity and MCID of the EQ-5D have not been formally assessed in CF.

Z-scores (used to assess BMI-for-age) were calculated by the manufacturer using growth charts from the US Centers for Disease Control and Prevention (CDC). A z-score is a statistical transformation that indicates *"how far away and in what direction (positive vs. negative) a measured value deviates from the population mean, expressed in units of the population standard deviation."*[53] For example, a patient with a z-score of –0.5 would have a BMI-for-age that is half a standard deviation below the population mean.

Sweat chloride is a biomarker for CFTR activity and the sweat chloride test is a standard diagnostic test for CF. Sweat chloride value ≥ 60 mmol/L is indicative of CF.[54]

Pulmonary exacerbation: In the ivacaftor studies, pulmonary exacerbation was defined as a new or change in antibiotic therapy (IV, inhaled, or oral) for any four or more of signs or symptoms, such as: 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 pulmonary function by 10%; and radiographic changes indicative of pulmonary infection.[13]

Harms examined included deaths, serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and adverse events (AEs). AEs of hepatic origin were considered as notable harms by the clinical expert consulted on this review and are included here.

3.2.5   Statistical Analysis

Sample size calculations were conducted in KONNECTION and STRIVE. In KONNECTION, enrolment of a minimum of 20 patients to a maximum of approximately 40 patients was planned. Sample sizes of 20 and 40 were capable of detecting a between-treatment difference of 5% in absolute change from baseline in per cent predicted FEV_1 with power of 85% and 99%, respectively. In STRIVE, enrolment of a minimum of 80 patients was planned. A sample size of 80 was sufficient to detect a between-treatment difference of 5% in absolute change from baseline in per cent predicted FEV_1 with a power of 88%. In ENVISION sample size was based on patient availability and not on any statistical consideration.

In KONNECTION, the primary efficacy end point was the absolute change from baseline in per cent predicted FEV_1 through week eight. In KONNECTION, the baseline value was defined as the most recent measurement collected prior to administration of the first dose of the study drug. This definition applied to all demographics and baseline characteristics. In addition, period baseline was defined as the most recent measurement collected prior to initial administration of study drug in each treatment period, with an additional requirement that the treatment period 2 baseline measurement be collected after 14 days in the washout period. If pre-dose measurement in treatment period 2 was missing, treatment period 1 baseline was used. This definition applied to all efficacy and safety data. Change from baseline was evaluated with respect to period baseline.

In STRIVE and ENVISION, the primary efficacy end point was the absolute change from baseline in per cent predicted FEV_1 through week 24.

In KONNECTION, the primary analysis for the primary efficacy outcome (per cent predicted FEV_1) was based on a mixed model repeated measure (MMRM) model with age and baseline per cent predicted FEV_1 as covariates. There was no imputation for missing data. Additional sensitivity analyses were conducted to assess the robustness of the primary analysis. These sensitivity analyses comprised different variance-covariance matrices in MMRM; non-parametric analysis: Wilcoxon signed rank-sum test; and analysis of covariance (ANCOVA). Also, to assess the impact of missing data on treatment effect estimated by MMRM analysis, the following sensitivity analyses were undertaken: last observation carried forward (LOCF)-based MMRM analysis; worst-case-based MMRM analysis and dropout-reason-based imputation MMRM analysis. In analysis based on worst case, missing data were imputed as the smallest post-baseline per cent predicted FEV_1 observation in the same period. In analysis based on dropout reason, missing data were imputed as the smallest post-baseline per cent predicted FEV_1 observation if reasons for premature termination of treatment were adverse event, noncompliance with study procedures, death, physician decision, or required prohibited medication and as LOCF for all other cases.

In KONNECTION, analyses of the secondary efficacy outcomes of sweat chloride and CFQ-R (respiratory domain) were similar to the primary analysis of the primary efficacy outcome, with the addition of baseline sweat chloride and baseline CFQ-R (respiratory domain) score as a covariate for sweat chloride and CFQ-R (respiratory domain) analyses respectively. Analyses of the secondary outcomes of weight and BMI were based on the linear mixed model (LMM) with age and per cent predicted FEV_1 as covariates. Sensitivity analyses described above for the primary efficacy outcome were not undertaken for the secondary efficacy outcomes.

In KONNECTION, the primary and key secondary end points were analyzed in sequence using a multi-stage gatekeeping procedure comprised of: Test 1 = primary efficacy end point tested at significance level alpha = 0.05; Test 2 = if statistically significant result was obtained from Test 1 then change from baseline in BMI over eight weeks and change from baseline in sweat chloride over eight weeks were tested using Hochberg's step-up procedure at significance level alpha = 0.05; and Test 3 = if statistically significant result was obtained from Test 2 then change from baseline in CFQ-R (respiratory domain) score was tested using Hochberg's step-up procedure.

In STRIVE, the primary analysis for the primary efficacy outcome (per cent predicted FEV_1 over 24 weeks) was based on a MMRM model. Adjustments were made for age and baseline per cent predicted FEV_1. There was no imputation for missing data. Additional sensitivity analyses were conducted to assess the robustness of the primary analysis. These sensitivity analyses comprised: different variance-covariance matrices in MMRM; non-parametric analysis: stratified Wilcoxon signed rank-sum test stratified by baseline age and FEV_1 status; and ANCOVA. Also, to assess the impact of missing data on treatment effect estimated by MMRM analysis, the following sensitivity analyses were undertaken: LOCF-based MMRM analysis; worst-case-based MMRM analysis; dropout-reason-based imputation MMRM analysis; and modelling the pattern of missing data. In the analysis based on worst case, missing data were imputed as the smallest post-baseline per cent predicted FEV_1 observation in the same period. In the analysis based on dropout reason, missing data were imputed as the smallest post-baseline per cent predicted FEV_1 observation if reasons for premature termination of treatment were adverse event, noncompliance with study procedures, death, physician decision, or required prohibited medication and as LOCF for all other cases. In the analysis based on the modelling pattern of missing data, if > 10% dropout rate or if there were inconsistencies in other sensitivity analyses, the impact of the dropout pattern on treatment effect and whether the missing data were random or not were assessed by pattern mixture model (PMM).

In STRIVE, analyses of the secondary efficacy outcomes of sweat chloride and CFQ-R (respiratory domain) were similar to the primary analysis of the primary efficacy outcome, with the addition of baseline sweat chloride and baseline CFQ-R (respiratory domain) score as a covariate for sweat chloride and CFQ-R (respiratory domain) analyses respectively. Analyses of the secondary outcome weight were based on the LMM with age and per cent predicted FEV_1 as covariates. In addition, sensitivity analyses were conducted for the secondary outcomes. For per cent predicted FEV_1 over 48 weeks, CFQ-R, and sweat chloride over 24 weeks, the following sensitivity analyses were conducted: ANCOVA with no imputation of missing data; ANCOVA with LOCF-based imputation; ANCOVA with worst-case-based imputation; ANCOVA with dropout-reason-based imputation and with PMM if dropout rate was > 10%.

In STRIVE, the primary and key secondary end points were analyzed in sequence using a multi-stage gatekeeping procedure comprised of: Test 1 = primary efficacy end point tested at significance level alpha = 0.05; Test 2 = if statistically significant result was obtained from Test 1 then change from baseline in CFQ-R (respiratory domain) score over 24 weeks and change from baseline in sweat chloride

over 24 weeks were tested using Hochberg's step-up procedure at significance level alpha = 0.05; and Test 3 = if statistically significant result was obtained from Test 2 then time to first pulmonary exacerbation over 48 weeks and change from baseline in weight at 48 weeks were tested using Hochberg's step-up procedure.

In ENVISION, the primary analysis for the primary efficacy outcome (per cent predicted FEV_1 over 24 weeks) was based on the MMRM model. Adjustments were made for baseline per cent predicted FEV_1. There was no imputation for missing data. Additional sensitivity analyses were conducted to assess the robustness of the primary analysis. These sensitivity analyses comprised: different variance-covariance matrices in MMRM; non-parametric analysis: stratified Wilcoxon signed rank-sum test stratified by baseline age and FEV_1 status; and ANCOVA. Also, to assess the impact of missing data on treatment effect estimated by MMRM analysis, the following sensitivity analyses were undertaken: LOCF-based MMRM analysis; worst-case-based MMRM analysis; dropout-reason-based imputation MMRM analysis; and modelling the pattern of missing data. Descriptions of worst-case- and dropout-reason-based analyses methods were similar to those for STRIVE. In the analysis based on the modelling pattern of missing data, if > 30% dropout rate, the impact of the dropout pattern on treatment effect and whether the missing data were random or not were assessed by PMM.

In ENVISION, analyses of the secondary efficacy outcomes of sweat chloride and CFQ-R (respiratory domain) were similar to the primary analysis of the primary efficacy outcome, with the addition of baseline sweat chloride and baseline CFQ-R (respiratory domain) score as a covariate for sweat chloride and CFQ-R (respiratory domain) analyses respectively. Analyses of the secondary outcome of weight were based on the LMM with per cent predicted FEV_1 as covariate.

In ENVISION, the primary and key secondary end points were analyzed in sequence using a multi-stage gatekeeping procedure comprised of: Test 1 = primary efficacy end point tested at significance level alpha = 0.05; Test 2 = if statistically significant result was obtained from Test 1 then change from baseline in weight at 24 weeks and change from baseline in sweat chloride over 24 weeks were tested using Hochberg's step-up procedure at significance level alpha = 0.05; and Test 3 = if statistically significant result was obtained from Test 2 then change from baseline in CFQ-R (respiratory domain) score over 24 weeks was tested using Hochberg's step-up procedure.

Event counts for change in acute pulmonary exacerbations and hospitalizations were analyzed by negative binomial regression in all three studies.

Several subgroup analyses were planned a priori and included subgroups based on age and baseline FEV_1 status, which are of interest for this review. Results for subgroups by age and baseline FEV_1 status were available for KONNECTION and STRIVE and subgroups by baseline FEV_1 status for ENVISION.

a) Analysis Populations
Full analysis set (FAS): In all three studies, the FAS was defined as all randomized patients who received at least one dose of study drug (ivacaftor or placebo). Patients were analyzed according to the study drug to which they were assigned.

Per protocol set (PPS): In KONNECTION, the PPS was defined as FAS patients without any major protocol violations. In STRIVE and ENVISION, the PPS was defined as all FAS patients without major protocol violations having at least 80% overall study drug compliance and having completed at least 80% of the

analysis period. In all three studies, major protocol violations were defined as violations that may have a major impact on efficacy assessments.

Safety set: In all three studies, safety set was defined as all randomized patients who received at least one dose of study drug (ivacaftor or placebo). Patients were analyzed according to the study drug they actually received.

3.3 Patient Disposition

In KONNECTION, 39 patients were randomized. This was a crossover study with 20 patients receiving ivacaftor and 19 patients receiving placebo in the first treatment period. Two patients in the initial ivacaftor treatment group and one patient in the initial placebo group discontinued treatment resulting in 18 patients crossing over to the placebo treatment group and 18 patients crossing over to the ivacaftor treatment group. Hence, in total there were 38 patients receiving ivacaftor and 37 patients receiving placebo. Stated reasons for discontinuation varied, but did not include a lack of efficacy (Table 5).

In STRIVE, a total of 167 patients were randomized, with six patients (one in the ivacaftor group and five in the placebo group) dropping out before receiving one dose of study medication. The FAS comprised 161 patients, within which 77 (92.8%) and 68 (87.2%) patients in the ivacaftor and placebo groups, respectively, completed 48 weeks of treatment. Stated reasons for discontinuation varied, but did not include a lack of efficacy (Table 5).

In ENVISION, a total of 52 patients were randomized equally between ivacaftor and placebo groups. The FAS comprised the randomized set, within which 26 (100.0%) and 22 (84.6%) patients in the ivacaftor and placebo groups, respectively, completed 48 weeks of treatment. Stated reasons for discontinuation varied, but did not include a lack of efficacy (Table 5).

At the end of the crossover study (KONNECTION, part 1), 36 patients were enrolled in the extension study (KONNECTION, part 2). At the end of 48 weeks, 75 (90.3%) patients from the ivacaftor group and 65 (82.1%) from the placebo group were enrolled in the extension trial (PERSIST [Study 105]) from STRIVE. All 26 (100.0%) patients from the ivacaftor group and 22 (84.6%) patients from the placebo group were enrolled in the extension trial (Study 105) from ENVISION after 48 weeks.

TABLE 5: PATIENT DISPOSITION

	KONNECTION (Study 111, part 1)		STRIVE (Study 102)		ENVISION (Study 103, part B)	
	Tx1 (IVA-PL)	Tx2 (PL-IVA)	IVA	PL	IVA	PL
Screened, N	42		NR		NR	
Randomized, N	20	19	84	83	26	26
Treated, N	38 (with IVA)[a]	37 (with placebo)[a]	83	78	26	26
Total discontinued[b], N (%)	2 (10)	1 (5.3)	6 (7.2)	10 (12.8)	0	4 (15.4)
Discontinuation reasons						
Lost to follow-up, N (%)	1 (5.0)	0 (0)	0	0	0	0
Adverse event	NA	NA	1 (1.2)	4 (5.1)	0	1 (3.8)
Noncompliance with study requirements	NA	NA	2 (2.4)	0	0	0

	KONNECTION (Study 111, part 1)		STRIVE (Study 102)		ENVISION (Study 103, part B)	
	Tx1 (IVA-PL)	Tx2 (PL-IVA)	IVA	PL	IVA	PL
Physician decision	NA	NA	0	1 (1.3)	0	0
Pregnancy	NA	NA	1 (1.2)	0	0	0
Requires prohibited medication	NA	NA	1 (1.2)	2 (2.6)	0	1 (3.8)
Withdrawal of consent	NA	NA	1 (1.2)	1 (1.3)	0	1 (3.8)
Other	1 (5.0)	1 (5.3)	0	2 (2.6)	0	1 (3.8)
FAS, N	20	19	83	78	26	26
PPS, N	11	15	69	64	24	20
Safety, N	20	19	83	78	26	26

FAS = full analysis set; IVA = ivacaftor; N = number of patients; NA = not applicable; PL = placebo; PPS = per protocol set; Tx1 = treatment sequence 1 = ivacaftor→ wash out→ placebo; Tx2 = treatment sequence 2 = placebo→ wash out→ ivacaftor.
[a] Two patients in the initial ivacaftor treatment group and one patient in the initial placebo group discontinued treatment resulting in 18 patients crossing over to the placebo group and 18 patients crossing over ivacaftor treatment group. Hence, in total there were 38 patients receiving ivacaftor and 37 patients receiving placebo.
[b] Treated patients who failed to complete treatment through eight weeks in KONNECTION and 48 weeks in STRIVE and ENVISION.
Source: Clinical Study Report-KONNECTION,[13] Clinical Study Report-STRIVE,[14] and Clinical Study Report-ENVISION.[15]

3.4   Exposure to Study Treatments

Extent of exposure to ivacaftor or placebo was comparable. In KONNECTION, exposure to study treatment (mean ± SD) was similar for patients receiving ivacaftor or placebo, being 54.7 ± 6.6 days for ivacaftor and 56.4 ± 2.1 days for placebo, at eight weeks.

In STRIVE, exposure to study treatment (mean ± SD) was 167.4 ± 17.8 days and 162.3 ± 32.0 days for ivacaftor and placebo groups, respectively, at 24 weeks, and 327.9 ± 50.0 days and 312.1 ± 78.9 days, respectively, at 48 weeks.

In ENVISION, exposure to study treatment (mean ± SD) was 169.5 ± 3.0 days and 154.8 ± 43.42 days for ivacaftor and placebo groups, respectively, at 24 weeks, and 336.5 ± 4.8 days and 299.3 ± 96.7 days, respectively, at 48 weeks.

Duration of exposure to concomitant standard CF medication was not explicitly stated.

3.5   Critical Appraisal
3.5.1   Internal Validity

KONNECTION, STRIVE and ENVISION were double-blind, randomized, placebo-controlled trials with appropriate randomization and allocation concealment through an interactive voice/web response system. In addition, KONNECTION had a crossover design so patients served as their own controls. Baseline characteristics were mostly similar across treatment groups in both STRIVE and ENVISION, except in a few instances. In ENVISION, compared with the placebo group, the ivacaftor group had fewer male patients (34.6% versus 61. 5%) and fewer patients with baseline $FEV_1 < 70\%$ (15.4% versus 30.8%). However, the overall baseline mean FEV_1 was similar in the ivacaftor and placebo groups, with 84.7% and 83.7% respectively. In STRIVE, compared with the placebo group, the ivacaftor group had fewer patients with prior use of the following medications: dornase alfa (65.1% versus 73.1%), tobramycin (33.7% versus 44.9%) and seretide (   ). Of note, the US Food and Drug Administration (FDA) review[36] considered the overall use of inhaled tobramycin in STRIVE patients to be lower than expected

for a relatively mature CF population in which colonization with *Pseudomonas aeruginosa* would be likely. In ENVISION, compared with the placebo group, the ivacaftor group had fewer patients with prior use of dornase alfa (████████████). However, the extent of bias these differences may have introduced is uncertain.

Analysis with the FAS was a modified intention-to-treat (ITT) analysis as the FAS included those patients who were randomized and who received at least one dose of study drug (ivacaftor or placebo).

Sensitivity analyses were conducted for the primary outcome of absolute change in per cent predicted FEV_1 from baseline using several methods. To assess the impact of missing data, additional sensitivity analyses were conducted using various methods for imputation of missing data. Results were consistent with the results of primary analysis.

Subgroup analyses were planned a priori. Results of subgroups categorized by age and subgroups categorized by FEV_1 status were available for KONNECTION and STRIVE, and results of subgroups by age were available for ENVISION.

In KONNECTION a crossover design was used, which has the advantage of having greater power when dealing with a limited patient population. However, period effects of crossover design have the potential of biasing results. Period effects could be due to patients having greater comfort and better knowledge at later periods and personnel acquiring greater skills at taking measurements at later periods. Also, carryover effects could impact results. In KONNECTION, the washout period was four to eight weeks. According to the clinical expert for this review, the duration of the washout period was appropriate.

The number of premature withdrawals in all three studies was small. However, there was a noticeable imbalance in the ENVISION trial, in which four (15.4%) patients in the placebo group withdrew prematurely compared with none in the ivacaftor group; it is uncertain to what extent this may have biased study results (i.e., potential risk of bias "for" or "against" treatment).

The duration of exposure to the study drug (ivacaftor or placebo) was reported in all three studies and was generally similar for both treatment groups. Concomitant standard CF medication was allowed; however, the duration of exposure to these medications was not reported. Hence, it was unclear if there was any imbalance in concomitant CF medication use in the two groups that could impact results.

In KONNECTION, the number of patients with each specific mutation was small (two to eight), hence the efficacy with respect to each specific mutation needs to be interpreted with caution.

Statistical analyses methods appear to be appropriate. No issues with respect to statistical analyses were raised by FDA[47] or Health Canada.[46]

3.5.2   External Validity

The majority of patients in all three studies were Caucasian and is reflective of the higher defective CF gene carrier rate in this ethnic group.

Patients with more severe disease (FEV_1 < 40%) were excluded from the studies, hence the results of these included studies are applicable to patients with mild to moderate CF. Of note, the FDA medical

reviewer considered the rationale given by the manufacturer (that it may be more difficult to detect changes in this subpopulation owing to severity and disease irreversibility) to be reasonable.[36] In KONNECTION, decline in per cent predicted FEV_1 during placebo treatment was 3.2% over eight weeks, which translates to a decline of 20.8% per year, which was greater than normally seen. Normally, with current practice there is a decline of 1% to 1.2% in per cent predicted FEV_1. The manufacturer could not definitively explain this, but thought it was likely due to the fact that the patient number was small. It is possible that the patients in KONNECTION were progressing more rapidly than the average CF population.

Inhaled tobramycin therapy was noted to be lower than expected, which could overestimate the added benefit of ivacaftor to standard care. However, the FDA reviewer[36] postulated that the lower-than-expected reported use of inhaled tobramycin may have been due to patients presenting while in an off-cycle period.

Patients using hypertonic saline as part of the CF treatment regimen were excluded. However, considering variations in mucolytic prescribing practice in Canada, this may not impact the generalizability of the findings.

Study results appear to be applicable to North American practice, given that North American patients comprised ≥ 50% of the patients in all three studies.

The comparator used in each trial was placebo, which was appropriate given ivacaftor's status as a first-in-class therapy.

3.6   Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 2). See Appendix 4: Detailed Outcome Data for detailed efficacy data.

3.6.1   Mortality

No deaths were reported in any of the three studies.

3.6.2   Per Cent Predicted FEV_1

Absolute change in per cent predicted FEV1 was the primary outcome in all three studies. The between-treatment differences in absolute change in per cent predicted FEV1 from baseline for ivacaftor versus placebo ranged between 9.99 and 12.45 and were statistically significant in all cases (Figure 2, Table 10). In KONNECTION, the mean absolute change in per cent predicted FEV1 through eight weeks was greater during ivacaftor treatment (7.49%) than during placebo (–3.19%) and the difference was statistically significant (P < 0.0001). Treatment differences were demonstrated by week 2 and were sustained through week 8 (Table 10). In STRIVE, the mean absolute change in per cent predicted FEV1 through 24 weeks was greater during ivacaftor treatment (10.39%) than during placebo (–0.18%) and the difference was statistically significant (P < 0.0001). The difference was sustained through week 48. In ENVISION, the mean absolute change in per cent predicted FEV1 through 24 weeks was greater during ivacaftor treatment (12.58%) than during placebo (0.13%) and the difference was statistically significant (P < 0.0001). The difference was sustained through week 48.

Subgroups by age category and FEV_1 status were analyzed (Table 11). In KONNECTION, between-treatment differences ███████████████████████████████████████ for age groups 12 to 17 years, and ≥ 18 years and for all categories of FEV_1 ███████████████████████████ for age group 6 to 11 years. In STRIVE for all age groups and for all categories of FEV_1, between-treatment differences

██ for 24 weeks and 48 weeks. In ENVISION, between-treatment differences █████████████████████████████████████ for subgroups with FEV$_1$ status: ≥ 70% to ≤ 90% and ≥ 90%, both over 24 weeks and 48 weeks. For the subgroup with FEV$_1$ status < 70% in ENVISION, the mean absolute change in FEV$_1$ from baseline and the between-treatment differences were not calculated due to ██ ████████████.

FIGURE 2: BETWEEN-TREATMENT DIFFERENCES FOR ABSOLUTE CHANGE IN PER CENT PREDICTED FEV$_1$ FOR IVA VERSUS PL

FEV$_1$ = forced expiratory volume in one second; PL = placebo; IVA = ivacaftor.

3.6.3   Pulmonary Exacerbation

In KONNECTION, the number of pulmonary exacerbation events was 10 (event rate = 0.16) during ivacaftor treatment and 10 (event rate = 0.20) for placebo; rate ratio (RR) = 0.81 (95% CI, 0.39 to 1.69). Of the reported pulmonary exacerbation ████████████ required hospitalization during ivacaftor and placebo treatments respectively, and █████████ of the total pulmonary exacerbations during ivacaftor and placebo treatments respectively required intravenous (IV) antibiotic treatment. Details are presented in Table 12.

In STRIVE, by week 24, 23 events were recorded in the ivacaftor group (event rate = 0.28) compared with 55 events in the placebo group (event rate = 0.74); RR = 0.38 (95% CI, 0.22 to 0.64). Of the reported pulmonary exacerbations experienced during ivacaftor and placebo treatment, 43% and 31% respectively required hospitalization, and 61% and 45% respectively required IV antibiotics. By week 48, 47 events were recorded in the ivacaftor group (event rate = 0.59) compared with 99 events in the placebo group (event rate = 1.38); RR = 0.43 (95% CI, 0.27 to 0.68). The proportions requiring

hospitalization and IV antibiotics were similar to those observed over 24 weeks. Details are presented in Table 12.

In ENVISION, the pulmonary exacerbation rate ratio of ivacaftor versus placebo ▮▮). In ENVISION, the rate ratio and 95% CI were not reported. Details are presented in Table 12.

3.6.4 Health-Related Quality of Life

In all three studies, CFQ-R was used to assess QoL and only the respiratory domain of CFQ-R was considered a secondary end point. However, results for the other domains of CFQ-R were also reported. In KONNECTION and STRIVE, the between-treatment differences in change in CFQ-R (respiratory domain) from baseline for ivacaftor versus placebo ranged between 8.08 and 9.63 and were statistically significant and in favour of ivacaftor (Figure 3, Table 13). In ENVISION, the between-treatment differences in change in CFQ-R (respiratory domain) from baseline for ivacaftor versus placebo ranged between 5.06 and 6.06 (for patient response) and between 4.88 and 5.93 (for parent or caregiver response) and were statistically not significant (Figure 3, Table 13). Subgroups by age category and FEV_1 status were also analyzed. In KONNECTION, results for CFQ-R (respiratory domain) were ▮▮▮▮▮▮▮▮▮ ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ for the age group ≥ 18 years and for all categories of FEV_1 and ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ for age groups: 6 to 11 years and 12 to 17 years. In STRIVE, results were ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ for all age groups and for all categories of FEV_1 for 24 weeks and 48 weeks. Results for the subgroups were ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ ▮▮▮▮▮▮▮▮▮▮▮▮▮. In ENVISION, results were ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ for subgroups with FEV_1 status: ≥ 70% to ≤ 90% and ≥ 90%, both over 24 weeks and 48 weeks. Results were not reported for various age subgroups or for the subgroup with FEV_1 < 70%. In all the studies, the magnitude of effect appears to be ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮. Details are presented in Table 14.

In KONNECTION (at eight weeks) and ENVISION (at 24 weeks and 48 weeks for both patient response and parent or caregiver response), the between-treatment differences in change in CFQ-R (non-respiratory domains) from baseline for ivacaftor versus placebo did not reach statistical significance for all the non-respiratory domains. The only exception was for the domain of weight at 48 weeks, where results were statistically significant in favour of ivacaftor. IN STRIVE, the between-treatment differences in change in CFQ-R (non-respiratory domains) from baseline for ivacaftor versus placebo were statistically significant for the physical, social, and eating domains at both 24 weeks and 48 weeks and treatment burden at 48 weeks. Results were ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ for the domains: emotion, body, and digestive at both 24 weeks and 48 weeks and treatment burden at 24 weeks. Details are presented in Table 15, Table 16, Table 17, and Table 18.

In addition, in STRIVE the QoL was also assessed using EQ-5D. The between-treatment differences in change in EQ-5D scores from baseline for ivacaftor versus placebo were 0.019 at 24 weeks and 0.018 at 48 weeks and were statistically significant in favour of ivacaftor. Details are presented in Table 19.

FIGURE 3: BETWEEN-TREATMENT DIFFERENCE IN CFQ-R (RESPIRATORY DOMAIN) FOR IVA VERSUS PL
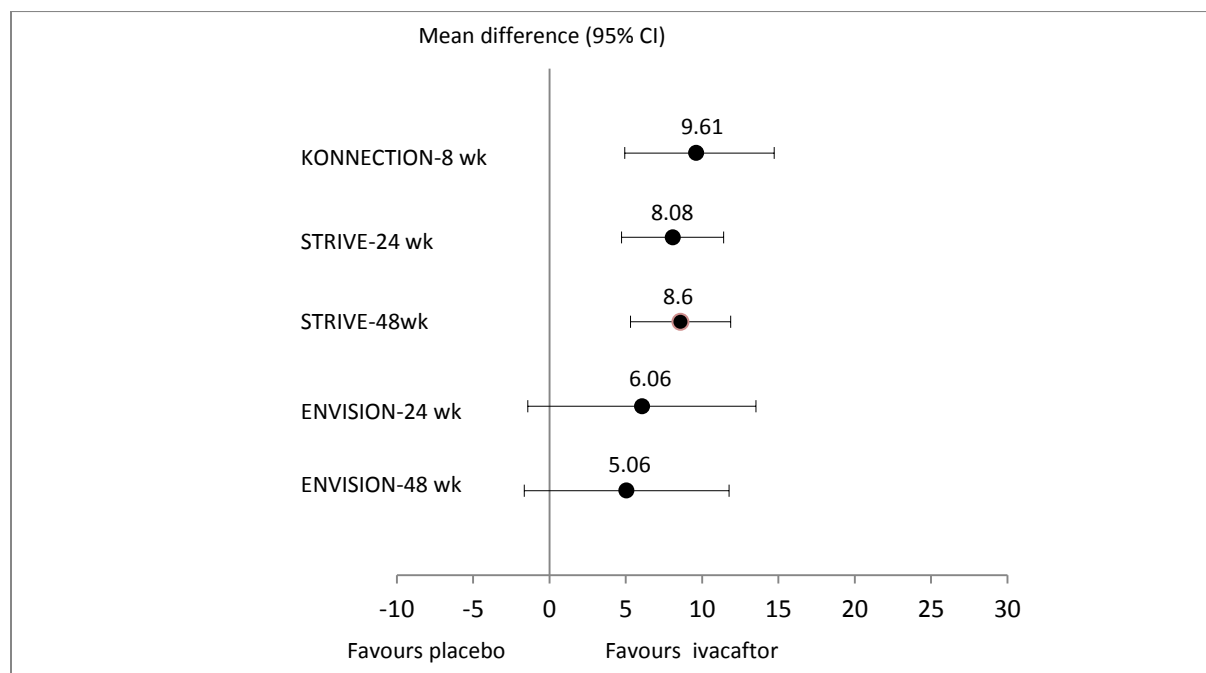
CFQ-R = Cystic Fibrosis Questionnaire-Revised; IVA =ivacaftor; PL = placebo.
Note: For ENVISION, the CFQ-R data are for patient response not parent/caregiver response.

3.6.5 Other Efficacy Outcomes
a) Hospitalization
In the three studies, overall hospitalization data were not reported. However, pulmonary exacerbations requiring hospitalization were reported. In STRIVE, over 48 weeks, 21 pulmonary exacerbation events among 11 patients on ivacaftor required hospitalization compared with 31 pulmonary exacerbation events among 23 patients on placebo requiring hospitalization. The rate ratio (95% CI) for pulmonary exacerbation requiring hospitalization for ivacaftor versus placebo was 0.64 (0.32, 1.26). In KONNECTION and ENVISION, the pulmonary exacerbation event rates requiring hospitalization were not reported and the rate ratios for ivacaftor versus placebo were also not reported but the *P* values reported indicated that the results were ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮. Details are presented in Table 12.

b) Body Mass Index and Weight
In the three studies, the between-treatment differences in changes in BMI (kg/m^2) from baseline for ivacaftor versus placebo ranged between 0.66 and 1.09 and were statistically significant and in favour of ivacaftor. In KONNECTION, the mean absolute change in BMI through eight weeks was greater during ivacaftor treatment (0.68) than during placebo (0.02) and the difference was statistically significant (*P* < 0.0001). In STRIVE, the mean absolute change in BMI through 48 weeks was greater during ivacaftor treatment (0.91) than during placebo (–0.02) and the difference was statistically significant (*P* < 0.0001). In ENVISION, the mean absolute change in BMI through 48 weeks was greater during ivacaftor treatment (1.34) than during placebo (0.23) and the difference was statistically significant (*P* = 0.0003). Details are presented in Table 20.

In the three studies, the between-treatment differences in changes in BMI-for-age z-score from baseline for ivacaftor versus placebo ranged between 0.28 to 0.45 respectively and were statistically significant and in favour of ivacaftor. Details are presented in Table 21.

In the three studies, the between-treatment differences in changes in weight (kg) from baseline for ivacaftor versus placebo ranged between 1.67 to 2.77 and were statistically significant and in favour of ivacaftor. In KONNECTION, the mean absolute change in weight (kg) through eight weeks was greater during ivacaftor treatment (2.01) than during placebo (0.34) and the difference was statistically significant (P = 0.0007). In STRIVE, the mean absolute change in weight (kg) through 48 weeks was greater during ivacaftor treatment (3.11) than during placebo (0.40) and the difference was statistically significant (P = 0.0001). In ENVISION, the mean absolute change in weight (kg) through 48 weeks was greater during ivacaftor treatment (5.85) than during placebo (3.08) and the difference was statistically significant (P = 0.0002). Details are presented in Table 22.

c)   Changes in Concomitant Medication
Changes in concomitant medication for ivacaftor versus placebo were not reported in any of the three studies.

d)   Sweat Chloride
In KONNECTION, the mean values of sweat chloride for ivacaftor were 93.37 mmol/L at baseline (N = 38) and 37.46 mmol/L post-baseline over eight weeks (N = 37), and the sweat chloride values for placebo (N = 37) were 94.23 mmol/L at baseline and 88.31 mmol/L post-baseline over eight weeks.

In STRIVE, the mean values of sweat chloride for ivacaftor (N = 78) were 100.35 mmol/L at baseline, 50.76 mmol/L post-baseline over 24 weeks, and 50.76 mmol/L post-baseline over 48 weeks; the mean values of sweat chloride for placebo (N = 74) were 100.13 mmol/L at baseline, 100.85 mmol/L post-baseline over 24 weeks, and 100.67 mmol/L post-baseline over 48 weeks.

In ENVISION, the mean values of sweat chloride for ivacaftor (N = 23) were 104.37 mmol/L at baseline, 47.91 mmol/L post-baseline over 24 weeks, and 47.29 mmol/L post-baseline over 48 weeks; the mean values of sweat chloride for placebo (N = 23) were 105.04 mmol/L at baseline, 104.65 mmol/L post-baseline over 24 weeks, and 103.84 mmol/L post-baseline over 48 weeks.

In all three studies, the between-treatment differences in changes in sweat chloride (mmol/L) from baseline for ivacaftor versus placebo ranged between –45.72 mmol/L and –54.32 mmol/L and were statistically significant and in favour of ivacaftor (Figure 4). Details are presented in Table 23. The proportion of ivacaftor-treated patients achieving a decrease in sweat chloride levels of ≥ 30% at 24 weeks was ███████████ in STRIVE and ENVISION respectively (Table 24), and the proportion of ivacaftor-treated patients achieving sweat chloride levels of < 60 mmol/L at 24 weeks was ███ in both STRIVE and ENVISION (Table 25).

FIGURE 4: BETWEEN-TREATMENT DIFFERENCE IN SWEAT CHLORIDE FOR IVA VERSUS PL; FAS
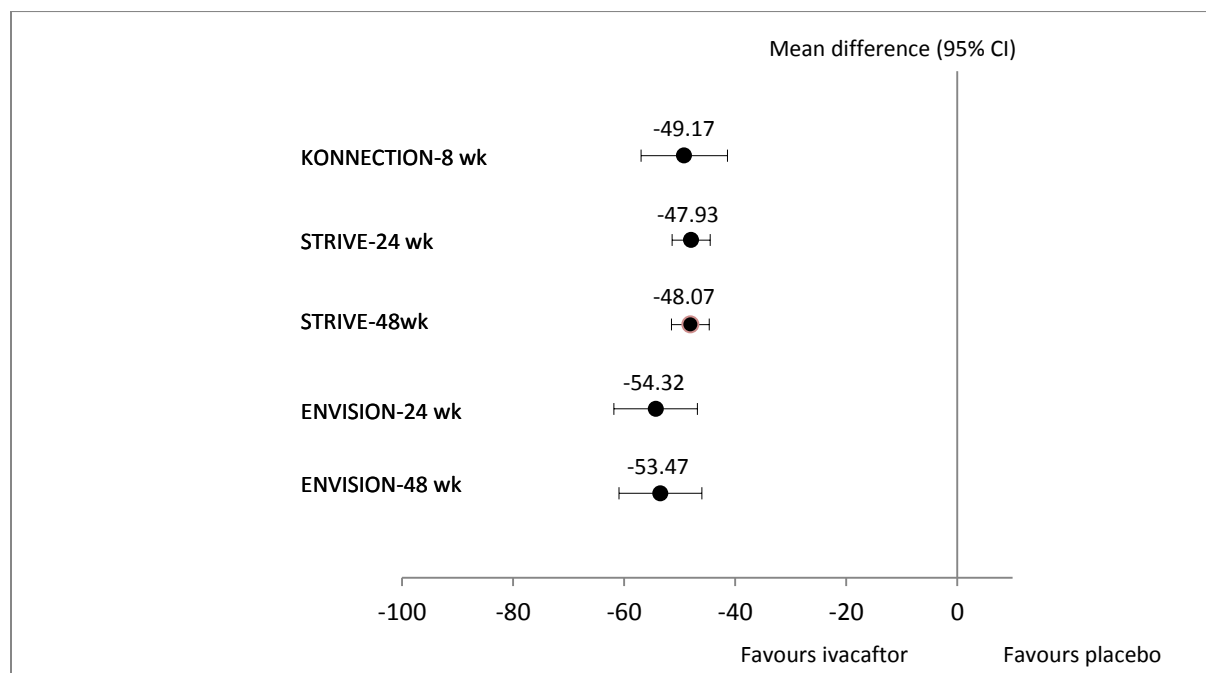
CI = confidence interval; FAS = full analysis set; PL = placebo; IVA = ivacaftor; wk = week.

e)   Efficacy Outcomes for Specific CFTR Non-G551D Gating Mutations
The KONNECTION study included only patients with CFTR non-G551D mutations. There were nine specific types. The mean absolute changes from baseline for ivacaftor-treated patients with each specific non-G551D mutation ranged between 3% and 20% for per cent predicted FEV_1, between 0.16 kg/m^2 and 1.62 kg/m^2 for BMI, between 3.3 and 20.0 for CFQ-R (respiratory domain) score, and between −6.25 mmol/L and −80.25 mmol/L for sweat chloride. Details are presented in Table 26. This study was not designed or powered to evaluate efficacy for specific non-G551 mutations. The number of patients with each specific mutation was small (two to eight) and hence any meaningful subgroup analysis is problematic. Also, changes from baseline for the individual mutations during placebo treatment were not provided, hence any analysis of between-treatment differences is not possible.

3.7   Harms
Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Appendix 4: Detailed Outcome Data for for detailed harms data.

3.7.1   Adverse Events
In KONNECTION, the percentage of patients experiencing AEs was higher during treatment with placebo compared to ivacaftor (83.3% versus 73.7%). In STRIVE, 98.8% of patients in the ivacaftor group experienced AEs compared with 100% in the placebo group. In ENVISION, 100% of patients in the ivacaftor group experienced AEs compared with 96.2% of patients in the placebo group. Respiratory-related AEs were among the most commonly occurring AEs. The incidence of pulmonary exacerbations of CF with ivacaftor versus placebo were, respectively, 23.7% versus 29.7% in KONNECTION; 41.0% versus 64.1% in STRIVE, and 30.8% in each group in ENVISION. Incidence of cough with ivacaftor versus placebo were, respectively, 13.2% versus 18.9% in KONNECTION; 32.5% versus 42.3% in STRIVE, and 50.0% versus 73.1% in ENVISION.

AEs that emerged numerically more often in the ivacaftor group compared with the placebo group in both STRIVE and ENVISION were headache (22.9% versus 16.7% in STRIVE; 26.9% versus 15.4% in ENVISION) and upper respiratory tract infection (22.9 % versus 15.4% in STRIVE; 23.1% versus 7.7% in ENVISION). In KONNECTION, headache emerged numerically less frequently in the ivacaftor group compared with the placebo group (7.9% versus 13.5%).

In KONNECTION, pyrexia (7.9% versus 2.7%) and fatigue (5.3% versus 0%) were numerically more frequent during ivacaftor treatment compared with placebo. In STRIVE, nasal congestion (20.5% versus 15.4%), rash (14.5% versus 5.1%), and dizziness (12.0% versus 1.3%) were numerically more frequent in the ivacaftor group compared with placebo. In ENVISION, oropharyngeal pain (26.9% versus 15.4%), nasopharyngitis (23.1% versus 7.7%), otitis media (15.4% versus 3.8%), diarrhea (11.5% versus 0%), and an increased eosinophil count (11.5% versus 3.8%) were numerically more frequent in the ivacaftor group compared with placebo. Details are presented in Table 6, Table 27, Table 28, and Table 29.

3.7.2   Serious Adverse Events

In the three studies, SAEs were higher with placebo compared to ivacaftor. In KONNECTON, 10.5% of patients experienced SAEs during treatment with ivacaftor compared with 21.6% of patients during treatment with placebo. In STRIVE, 24.1% of patients in the ivacaftor group experienced SAEs compared with 42.3% in the placebo group. In ENVISION, 19.2% of patients in the ivacaftor group experienced SAEs compared with 23.1% of patients in the placebo group. SAEs were largely due to pulmonary exacerbations. SAEs resulting from pulmonary exacerbation in the ivacaftor group versus the placebo group were 5.3% versus 5.4% in KONNECTION; 13.3% versus 33.3% in STRIVE, and 7.7% versus 11.5% in ENVISION. Details are presented in Table 6, Table 27, Table 28, and Table 29.

3.7.3   Withdrawals Due to Adverse Events

In KONNECTION, there were no withdrawals due to adverse events (WDAEs), and in both STRIVE and ENVISION WDAEs were infrequent. In STRIVE, only 1 (1.2%) patient withdrew due to AEs from the ivacaftor group compared with 4 (5.1%) from the placebo group. In ENVISION, no patients withdrew due to AEs from the ivacaftor group while AEs resulted in 1 (3.8%) patient withdrawing from the placebo group. Details are presented in Table 6, Table 27, Table 28, and Table 29.

TABLE 6: HARMS

Outcome	KONNECTION (8 Weeks)		STRIVE (48 Weeks)		ENVISION (48 Weeks)	
	IVA (N = 38) n (%)	PL (N = 37) n (%)	IVA (N = 83)	PL (N = 78)	IVA (N = 26)	PL (N = 26)
Any AE	28 (73.7)	31 (83.8)	82 (98.8)	78 (100.0)	26 (100.0)	25 (96.2)
AE in > 20% of patients[a]						
Pulmonary exacerbation of CF	9 (23.7)	11 (29.7)	34 (41.0)	50 (64.1)	8 (30.8)	8 (30.8)
Cough	-	-	27 (32.5)	33 (42.3)	13 (50.0)	19 (73.1)
Headache	-	-	19 (22.9)	13 (16.7)	7 (26.9)	4 (15.4)
Upper respiratory tract infection	-	-	19 (22.9)	12 (15.4)	6 (23.1)	2 (7.7)
Nasal congestion	-	-	17 (20.5)	12 (15.4)	-	-
Oropharyngeal pain	-	-	17 (20.5)	15 (19.2)	7 (26.9)	4 (15.4)
Hemoptysis	-	-	9 (10.8)	17 (21.8)	NR	NR
Nasopharyngitis	NR	NR	-	-	6 (23.1)	2 (7.7)
Pyrexia	-	-	-	-	6 (23.1)	7 (26.9)
SAE	4 (10.5)	7 (18.9)	20 (24.1)	33 (42.3)	5 (19.2)	6 (23.1)
WDAE	0 (0)	0 (0)	1 (1.2)	4 (5.1)	0	1 (3.8)

AE = adverse event; CF = cystic fibrosis; IVA = ivacaftor, n = number of patients with event; N = number of patients;
PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] If AE ≤ 20% then data not reported here and indicated by -.
Source: Clinical Study Report-KONNECTION,[13] Clinical Study Report-STRIVE,[14] and Clinical Study Report-ENVISION.[15]

3.7.4 Notable Harms

Hepatic AEs were examined as suggested by the clinical expert consulted for this review. In KONNECTION, STRIVE, and ENVISION, numbers of AEs that could signal possible hepatic harms were small in number overall, with no clear pattern emerging between groups. Hepatic AEs, such as increased ALT, AST, GGT, and hepatic enzymes were examined. A single case of hepatic enzyme elevation was noted as an SAE in the placebo group only in KONNECTION, and in the ivacaftor group only in ENVISION. A single case of hepatic enzyme elevation was noted as a WDAE in the ivacaftor group only in STRIVE. A single case of ALT increase was noted as a WDAE in the placebo group only in STRIVE. Details are presented in Table 30, Table 31, and Table 32.

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review comes from three phase 3, double-blind, randomized, placebo-controlled studies (KONNECTION, STRIVE, and ENVISION), together comprising 251 patients with CF of mild to moderate severity (FEV$_1$ ≥ 40% predicted) and specific gating mutations. STRIVE and ENVISION included patients with a G551D mutation in at least one allele while KONNECTION included patients without a G551D mutation but with one of the following mutations in at least one allele: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R. KONNECTION and STRIVE both included a mixed population of pediatric and adult patients and ENVISION included only pediatric patients. KONNECTION was a crossover study of 20 weeks to 24 weeks' duration comprised of ivacaftor or placebo for eight weeks, followed by a four to eight week washout period followed by crossover to an additional eight weeks of ivacaftor or placebo. Both STRIVE and ENVISION had a duration of 48 weeks. In all three studies the ivacaftor dose was a 150 mg tablet once every 12 hours and patients were recommended to continue with their stable medications for CF except hypertonic saline, which was not allowed. The primary efficacy outcome was absolute change from baseline in per cent predicted FEV$_1$ in the three studies.

The studies were generally well conducted with no major methodological issues identified. The studies were appropriately blinded with allocation concealment by interactive voice/web response system. There were few dropouts. KONNECTION being a crossover study, patients served as their own controls. Baseline characteristics were generally similar across treatment groups in STRIVE and ENVISION. The clinical expert consulted on this review confirmed that the efficacy outcomes included in the studies and the CDR systematic review are clinically relevant. The use of a placebo comparator was considered appropriate, given the first-in-class therapy status of ivacaftor. Studies were not of sufficient size or duration to examine survival as an end point.

Generalizability of the findings is limited to patients with mild to moderate severity CF who are at least six years old. It is unknown to what extent these findings apply to younger patients or to those with more severe disease. Of note, although the inclusion criteria extended to the elderly (≥ 65 years), there were no patients actually recruited in the ≥ 65 years age group, hence the applicability of the findings in this age group is uncertain. However, this may be of minor concern since there are few older CF patients. Patients with severe renal and hepatic disease were excluded from the studies; hence, the applicability of the findings to these patient groups is uncertain.

4.2 Interpretation of Results

4.2.1 Efficacy

Given the relatively small sample size and limited duration (eight weeks or 48 weeks) of the included studies, the reviewed studies were not able to demonstrate a survival advantage or disadvantage for ivacaftor compared with placebo. Rather, the evaluation of efficacy is limited to the use of surrogate end points, including per cent predicted FEV$_1$, the incidence of pulmonary exacerbations, and weight changes. However, the clinical expert considered that the selected outcomes were appropriate, given that maintenance of pulmonary function (higher FEV$_1$) and fewer respiratory exacerbations have been associated with increased survivorship.

The reviewed studies were consistent in demonstrating statistically significant improvements in pulmonary function for ivacaftor versus placebo, as measured by changes in FEV$_1$, and symptoms

captured in the respiratory domain of the CFQ-R. Specifically, the three included studies reported a mean increase in per cent predicted FEV_1 of ≥ 10% with ivacaftor compared with placebo. While no published information on the MCID in FEV_1 in CF was identified by CDR, the clinical expert consulted for this review indicated that a change of this magnitude is considered clinically meaningful and that improvement in FEV_1 leads to better survivorship. Further, between-treatment differences in patient-reported respiratory symptoms favouring ivacaftor over placebo are supportive of FEV_1 findings. The statistically significant improvements in patient-reported respiratory symptoms achieved with ivacaftor, as measured by the CFQ-R in KONNECTION and STRIVE, exceed the MCID. Finally, ivacaftor produced statistically significantly greater gains in body weight and BMI-for-age z-scores and greater reductions in sweat chloride compared with placebo in the three trials. At 24 weeks, a large proportion of ivacaftor-treated patients achieved sweat chloride levels of < 60 mmol/L (77% of both STRIVE and ENVISION patients) or a ≥ 30% reduction (93% and 86% in STRIVE and ENVISION respectively); however, according to the clinical expert consulted for this review, decrease in sweat chloride alone should not be considered as an indicator of improvement. Researchers have proposed that sweat chloride concentrations could be a potential outcome measure in the study of drugs targeting CFTR gene dysfunction;[55,56] however, it does not appear that drug-associated changes in sweat glands (resulting in a reduction in sweat chloride levels) correlate with changes in respiratory function.[55,56]

Patients with one of the nine non-G551D mutations (G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R) were few in number (two to eight), hence efficacy results for the individual mutation types should be interpreted with caution. Of note, FDA did not approve ivacaftor for G970R mutation.

To investigate the robustness of efficacy results obtained by FAS analyses, several sensitivity analyses as well as PPS analyses were conducted and efficacy results were found to be consistent.

The investigators performed a post-hoc analysis[16] to determine whether the response with ivacaftor was consistent across various patient groups with different FEV_1 responses to ivacaftor. In this post-hoc analysis[16] of patients (N = 209) from STRIVE and ENVISION who received 48 weeks of ivacaftor or placebo, patients were divided into tertiles according to FEV_1 response (lower, middle, and upper). For each tertile, efficacy of ivacaftor group was compared with the corresponding tertile placebo group as well with the overall placebo group. Efficacy was assessed in terms of sweat chloride, body weight, pulmonary exacerbation, and CFQ-R (respiratory domain) score. Results of the analyses suggested that in most cases the patients in the various FEV_1 response tertiles had the potential to benefit from treatment with ivacaftor. Details are presented in Table 33.

Two open-label extension studies (KONNECTION part 2 enrolling patients who completed part 1 of KONNECTION and PERSIST enrolling patients who completed either STRIVE or ENVISION) were conducted. Overall, the efficacy results through 24 weeks in part 2 were supportive of those observed over eight weeks of treatment in part 1 (Table 34). Sustained effects and improvements in FEV_1 per cent predicted, CFQ-R respiratory domain, and body weight observed in PERSIST among patients who continued ivacaftor were consistent with those of the ivacaftor group from the preceding 48-week RCTs. Improvements in FEV_1, QoL, and weight in the placebo-ivacaftor group were similar to those seen in the ivacaftor group of STRIVE and ENVISION (Table 36). Limitations of these open-label observational findings largely stem from the lack of a comparator group. Therefore, the extension data are suggestive of durability of response to ivacaftor, but they lack sufficient rigour to conclude this with confidence.

A recent systematic review[57] on ivacaftor for treatment of CF patients with G551D mutation included two RCTs: STRIVE and ENVISION and the open-label extension study with patients from these two RCTs. The authors concluded that the available evidence suggested that for CF patients with G551D mutation, treatment with ivacaftor was clinically effective. They noted that the high cost of ivacaftor may prove to be an impediment to uptake of the treatment and that further research to explore long-term effects of ivacaftor should be undertaken.

Ivacaftor is a first-in-class drug, thus comparison with placebo was considered by the CDR reviewer to be appropriate; however, it is important to note that ivacaftor was studied as add-on to a stable regimen of CF medications. There is no RCT evidence to suggest that ivacaftor may replace or minimize the need for current treatments. Thus the availability of ivacaftor is not expected to reduce the time patients must spend administering other treatments.

It is unclear from the studies the extent to which concomitant medication use was optimized in the reviewed studies. The FDA reviewer[36] considered the overall use of inhaled tobramycin in STRIVE patients to be lower than expected for a relatively mature CF population in which colonization with *Pseudomonas aeruginosa* would be likely. Less than optimal concomitant therapy could have overestimated the benefit to be obtained with ivacaftor.

4.2.2   Harms

There were no deaths reported in any of the three included studies. SAEs were numerically less frequent in the ivacaftor compared with placebo group, with CF lung exacerbations representing the most commonly encountered SAE in the studies; of note, the FDA considered the SAE data consistent with what would be expected in a CF population.[36] WDAEs were infrequent in the included studies, with one ivacaftor-treated patient withdrawing due to an adverse event in the STRIVE study only. AEs most commonly observed in the ivacaftor groups included upper respiratory tract infection, headache, dizziness, and rash.

The FDA review[36] of ivacaftor similarly reported no safety concerns and did not ask for a post-marketing Risk Evaluation and Mitigation Strategy (REMS) from the manufacturer; however, the FDA did recommend more frequent monitoring of liver function during initial treatment with ivacaftor, noting the CF population's underlying risk for elevations in liver function tests.[36] The Health Canada approved product monograph recommends baseline and periodic evaluations of liver transaminases be performed.

Ivacaftor is a substrate for CYP 3A4, and as such, carries with it the potential for significant drug-to-drug interactions with CYP 3A4 inhibitors and inducers, such as with ketoconazole and rifampin. Moreover, ivacaftor and its M1 metabolite may inhibit medications metabolized by CYP 3A4 and P-glycoprotein (P-gp).[5] The Health Canada approved product monograph recommends against using ivacaftor in combination with strong CYP 3A inhibitors, and advises caution and appropriate monitoring when co-administering ivacaftor with CYP 3A or P-gp substrates. By virtue of being both a substrate for and possible inhibitor of CYP 3A4, ivacaftor is susceptible to numerous drug-to-drug interactions; to clarify uncertainty around the potential for P-glycoprotein mediated drug-to-drug interactions, the FDA asked the manufacturer to conduct a post-marketing study.

Since ivacaftor is a first-in-class medication, there are no other relevant comparators against which to compare harms information.

4.3   Other Considerations

Ivacaftor has been studied in patients homozygous for the more common, F508del-CFTR mutation in a 16-week randomized, double-blind, placebo-controlled parallel-group trial, but was not found to be effective in this CF population.

Planned, ongoing or recently completed studies are likely to provide further insights into efficacy and safety of ivacaftor treatment in CF patients. Six such studies[6-11] on CF patients with a gating mutation were identified. One study[8] is open but not recruiting patients, four studies[6,9-11] are recruiting patients, and one study[7] is completed but at this time results are not yet available. Of these six studies, two studies[7,9] are specifically on CF patients younger than six years of age, a patient group for whom currently information regarding effect of ivacaftor treatment is lacking. One study[7] is an open-label study evaluating the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in children with CF who are two through five years of age and have a CFTR gating mutation in at least one allele; the other study[9] is an open-label study on CF patients younger than six years of age with a CFTR gating mutation in at least one allele and the goal is to evaluate the long-term safety and pharmacodynamics of ivacaftor treatment and to explore efficacy of long-term ivacaftor treatment. A randomized, double-blind, crossover study[6] will investigate short-term effects of ivacaftor on sweat chloride concentration and lung function in CF patients aged two years and older with mutations other than G551D. A randomized, double-blind, crossover phase 4 study[8] will investigate if ivacaftor will restore CFTR function in treated CF patients aged 16 to 70 years with the G551D mutation. A phase 3, two-arm, open-label, rollover study)[10] will evaluate the safety of long-term ivacaftor treatment in CF patients six years of age and older and with a non-G551D CFTR mutation. A longitudinal study[11] will assess energy expenditure, weight gain, body composition, and lung function in CF patients aged six years and older with a gating mutation before treatment and after three months treatment with ivacaftor.

FDA has not approved ivacaftor treatment for CF patients with a G970R mutation.

5. CONCLUSIONS

Compared with placebo, ivacaftor showed a consistent, statistically significant and clinically meaningful improvement in per cent predicted FEV_1 from baseline through eight weeks for KONNECTION and through 24 weeks and 48 weeks for STRIVE and ENVISION across the spectrum of pediatric and adult populations studied. The magnitude of effect observed (~ 10%) was achieved when ivacaftor was used as an add-on therapy to a stable regimen of CF therapies. In addition, ivacaftor treatment demonstrated statistically significant and clinically meaningful improvements in patient-reported respiratory symptoms as measured by the CFQ-R in KONNECTION and STRIVE. Compared with placebo, a statistically significant greater weight gain was observed with ivacaftor in all three studies. There were no significant differences between ivacaftor and placebo with respect to pulmonary exacerbation requiring hospitalization.

Ivacaftor treatment resulted in few WDAEs and SAEs. Nonetheless, baseline and periodic monitoring of liver transaminases are recommended by the FDA and Health Canada, given this population's underlying risk for elevations in liver enzymes. Comparative information beyond 48 weeks is lacking but open-label extension studies suggest sustained efficacy based on per cent predicted FEV_1, CFQ-R (respiratory domain), weight, and BMI. Also, no additional safety signals were identified.

Findings from these studies are applicable to patients aged six years or older with mild to moderate CF (FEV_1 > 40% predicted) and having a G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R mutation on at least one allele. There is no available RCT evidence regarding the efficacy of ivacaftor in patients having a CFTR mutation who are less than six years or age, or who have more severe disease (FEV_1 < 40% predicted).

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

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

One patient group — Cystic Fibrosis Canada (CF Canada) — provided a patient input submission for Kalydeco. CF Canada is a charitable non-profit corporation with a mission to help people with cystic fibrosis (CF). CF Canada funds research toward the goal of a cure or control for CF, supports high-quality CF care, and promotes public awareness of CF. Since its establishment, CF Canada has invested more than $150 million in leading research and care. For the 2013-2014 financial year, CF Canada received financial contributions from Abbott, Gilead, Hoffman-La Roche, Merck, Novartis, Vertex, and Rx&D. Contributions from pharmaceutical companies accounted for about one and a half per cent of the organization's gross revenue in 2013–2014.

2. Condition- and Current Therapy-related Information

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

CF is an inherited genetic disorder primarily affecting the lungs and digestive system. Currently, 4,000 Canadians have CF, of which 15 patients have one of the following gating mutations: *G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D,* and *G970R*. The disease causes the body to produce thick, sticky mucous that is difficult to clear from the lungs, resulting in persistent infections, progressive scarring of the airways and a decline in lung function. Respiratory failure is the primary cause of death in CF patients. Of the 43 CF patients who died in 2012, half were under 32 years old.

Due to the lack of pancreatic enzymes, CF patients have difficulty digesting fats and proteins and are vitamin deficient and thus have difficulty gaining weight. They may also become diabetic and require insulin therapy.

Patients experience chronic coughing, which results in lung pain, and decreased energy. They often have limited physical abilities and do not have the energy to enjoy time with their families and friends, to complete their education or maintain employment, or even to travel. If a patient's condition worsens, a hospital stay of at least two weeks may be required and there may be a need for oxygen therapy at some point.

Being a caregiver for a CF patient can have significant emotional, psychological, physical, and financial impacts. (Note: the remainder of this paragraph is copied from the Patient Input Summary for the Kalydeco submission received September 21, 2012.) As CF is an inherited disorder, parents tend to blame themselves for their child's condition and for not giving them the opportunity to have a normal childhood. Caregivers may feel helpless watching their loved ones as they cough relentlessly and bring up thick mucous and phlegm. In order to accommodate treatments for a loved one with CF, caregivers change their daily routine, social activities and possibly even their employment. Caregivers may even incur repetitive strain injuries while assisting with physical therapies for a child or loved one with CF. Finally, paying for costly treatments, particularly those administered at home, can put significant financial strain on the caregiver.

Currently, there is no cure for CF. Kalydeco is now available for treatment of CF patients with the G551D mutation. Most CF patients take pancreatic enzymes, multivitamins, and nutritional supplements daily to maintain normal growth. Patients perform airway clearance techniques, which include physiotherapy and exercises, at least twice a day for about 30 to 45 minutes per session to improve the clearance of secretions from their lungs. The total time spent on maintaining lung health exceeds two hours per day and can take as long seven hours. Inhaled medications are used to open the airways, while inhaled, intravenous, or oral antibiotic treatments are used to control infections. Development of antibiotic resistance is common, limiting treatment options.

Persistent infections eventually destroy the lungs and while lung transplantation may help end-stage CF patients, the extended median life expectancy is only 34 months following a lung transplant.

3. Related Information About the Drug Being Reviewed

Kalydeco is an oral targeted therapy that treats the underlying cause of CF.

Based on their understanding of Kalydeco, a number of people living with CF and their families have indicated that they expect it will improve lung function, weight gain, and in many cases, help to avoid the need for lung transplantation. A mother of twins with CF stated, "We believe that our nine-year-old twin sons could benefit from Kalydeco because it will help maintain and possibly improve their lung function, therefore decreasing their hours of treatments. This drug can help them gain weight so they could avoid gastrostomy tube feedings. Receiving their nutrition like other children do will make them feel more normal."

Those who have been on Kalydeco either through clinical trials or private insurance have reported improvements in lung function and weight gain. The improvements in health have also led to better QoL and ability to function normally. A parent of two children with CF reported that, "Since my son and daughter have been on Kalydeco, there has been a significant difference in their lives. Before they were on this drug, they were regularly in hospital for treatment for lung infections requiring intravenous intervention. They had to take more medication daily and the inhaled medication alone took two hours per day. Now with Kalydeco, they are healthy and their lives are more stable and predictable. My son is able to play like a normal child. He could not keep up with his friends before he started taking Kalydeco. My daughter can now do sleepovers without extra equipment and demands on others. Imagine thinking your child's diagnosis is to live not much more than your current age. Now with Kalydeco, normal life expectancy is possible and expected!"

4. Additional Information

Since being approved for use in Canada, over 20 individuals have access to Kalydeco through their private insurance. As of the date of this submission, the drug has been approved for reimbursement by the public drug programs in Ontario and Alberta for people with CF ages six and over with the G551D mutation.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present
	MEDLINE Daily and MEDLINE 1946 to present
	MEDLINE In-Process & Other Non-Indexed Citations
	Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of search:	July 14, 2014
Alerts:	Weekly search updates until November 19, 2014
Study types:	No search filters were applied
Limits:	No date or language limits were used
	Human filter was applied
	Conference abstracts were excluded

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

MULTI-DATABASE STRATEGY	
#	Searches
1	(Kalydeco* or ivacaftor* or UNII-1Y740ILL1Z or VX 770 or VX770).ti,ot,ab,sh,hw,rn,nm.
2	(873054-44-5 or 1134822-00-6 or 1174930-71-2).rn,nm.
3	1 or 2
4	3 use pmez
5	*ivacaftor/
6	(Kalydeco* or ivacaftor* or UNII-1Y740ILL1Z or VX 770 or VX770).ti,ab.
7	5 or 6
8	7 not conference abstract.pt.
9	8 use oemezd
10	4 or 9
11	exp animals/
12	exp animal experimentation/ or exp animal experiment/
13	exp models animal/
14	nonhuman/
15	exp vertebrate/ or exp vertebrates/
16	animal.po.
17	or/11-16
18	exp humans/
19	exp human experimentation/ or exp human experiment/
20	human.po.
21	or/18-20
22	17 not 21
23	10 not 22
24	remove duplicates from 23

OTHER DATABASES	
PubMed	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:	July 2014
Keywords:	Kalydeco, 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 evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Davies J, et al.[58]	Phase 2; not pivotal
Rowe SM, et al.[59]	Phase 2; not pivotal
Accurso FJ, et al.[60]	Phase 2; not pivotal
CSR-101[61]	Phase 2; not pivotal
CSR-106[62]	Phase 2; not pivotal

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 7: CONCOMITANT MEDICATION RECEIVED BY AT LEAST 15% OF PATIENTS IN KONNECTION (PART 1); FAS

Concomitant Drug (WHO Drug Dictionary Classification)	IVA, N (%)	PL, N (%)
Patients with any concomitant medication	▮	▮
Dornase alfa	▮	▮
Pancreatin	▮	▮
Azithromycin	▮	▮
Salbutamol	▮	▮
Seretide	▮	▮
Vitamins NOS w/zinc	▮	▮
Colecalciferol	▮	▮
Sodium chloride	▮	▮
Bactrim	▮	▮
Ibuprofen	▮	▮
Macrogol	▮	▮
Tocopheryl acetate	▮	▮
Tobramycin	▮	▮
Colistimethate sodium	▮	▮
Paracetamol	▮	▮
Fluticasone propionate	▮	▮
Levosalbutamol hydrochloride	▮	▮
Omeprazole	▮	▮
Vitamin D NOS	▮	▮
Amoxi-Clavulanico	▮	▮
Multivitamins with minerals/90003801/	▮	▮
Influenza vaccine	▮	▮
Levofloxacin	▮	▮

FAS = full analysis set; IVA = ivacaftor; n = number of patients with event; PL = placebo; WHO = World Health Organization.
Source: KONNECTION Clinical Study Report.[13]

TABLE 8: CONCOMITANT MEDICATION RECEIVED BY AT LEAST 15% OF PATIENTS IN STRIVE (48 WEEKS); FAS

WHO Drug Dictionary Classification	IVA n (%)	PL n (%)
Patients with any concomitant medication	83 (100.0)	78 (100.0)
Pancrelipase	74 (89.2)	74 (94.9)
Dornase alfa	57 (68.7)	57 (73.1)
Azithromycin	57 (68.7)	55 (70.5)
Tobramycin	41 (49.4)	54 (69.2)
Adeks/01439301/	45 (54.2)	46 (59.0)
Salbutamol	38 (45.8)	43 (55.1)
Ciprofloxacin	31 (37.3)	43 (55.1)
Seretide/01420901/	24 (28.9)	36 (46.2)
Paracetamol	30 (36.1)	22 (28.2)
Ibuprofen	25 (30.1)	22 (28.2)
Omeprazole	27 (32.5)	20 (25.6)
Sodium chloride	27 (32.5)	16 (20.5)
Influenza vaccine	19 (22.9)	20 (25.6)
Salbutamol sulfate	19 (22.9)	17 (21.8)
Bactrim/00086101/	17 (20.5)	18 (23.1)
Tocopherol	20 (24.1)	12 (15.4)
Vitamin D Nos	20 (24.1)	12 (15.4)
Multivitamins	16 (19.3)	12 (15.4)
Fluticasone propionate	13 (15.7)	14 (17.9)
Levofloxacin	13 (15.7)	14 (17.9)
Ceftazidime	8 (9.6)	17 (21.8)
Meropenem	7 (8.4)	16 (20.5)
Vitamin K Nos	12 (14.5)	11 (14.1)
Aztreonam	8 (9.6)	13 (16.7)
Colecalciferol	13 (15.7)	8 (10.3)
Macrogol	8 (9.6)	13 (16.7)
Co-trimoxazole	7 (8.4)	13 (16.7)
Prednisone	6 (7.2)	14 (17.9)
Montelukast sodium	6 (7.2)	13 (16.7)
Minocycline	0	14 (17.9)

FAS = full analysis set; IVA = ivacaftor; n = number of patients with event; PL = placebo; WHO = World Health Organization.
Source: STRIVE Clinical Study Report.[14]

TABLE 9: CONCOMITANT MEDICATION RECEIVED BY AT LEAST 15% OF PATIENTS IN ENVISION (48 WEEKS); FAS

WHO Drug Dictionary Classification	IVA n (%)	PL n (%)
Patients with any concomitant medication	**26 (100.0)**	**26 (100.0)**
Pancrelipase	25 (96.2)	25 (96.2)
Dornase alfa	18 (69.2)	22 (84.6)
Azithromycin	15 (57.7)	14 (53.8)
Tobramycin	13 (50.0)	13 (50.0)
ADEKS/01439301/	11 (42.3)	14 (53.8)
Salbutamol	12 (46.2)	12 (46.2)
Paracetamol	14 (53.8)	7 (26.9)
Sodium chloride	8 (30.8)	9 (34.6)
Ciprofloxacin	6 (23.1)	8 (30.8)
Ibuprofen	8 (30.8)	5 (19.2)
Seretide/01420901/	5 (19.2)	7 (26.9)
Amoxicillin with clavulanate potassium	6 (23.1)	5 (19.2)
Augmentin/00756801/	5 (19.2)	6 (23.1)
Bactrim/00086101/	2 (7.7)	9 (34.6)
Co-Trimoxazole	6 (23.1)	5 (19.2)
Salbutamol sulfate	6 (23.1)	5 (19.2)
Cetirizine hydrochloride	4 (15.4)	6 (23.1)
Lansoprazole	5 (19.2)	5 (19.2)
Mometasone furoate	4 (15.4)	6 (23.1)
Omeprazole	5 (19.2)	5 (19.2)
Influenza vaccine	3 (11.5)	6 (23.1)
Macrogol	5 (19.2)	4 (15.4)
Cholecalciferol	4 (15.4)	4 (15.4)
Colistin	3 (11.5)	5 (19.2)
Fat/Carbohydrates/Proteins/Minerals/Vitamins	2 (7.7)	6 (23.1)
Timentin/00703201/	3 (11.5)	5 (19.2)
Fluticasone propionate	2 (7.7)	5 (19.2)
Ursodeoxycholic acid	3 (11.5)	4 (15.4)
Flucloxacillin	4 (15.4)	2 (7.7)
Montelukast sodium	2 (7.7)	4 (15.4)
Ranitidine hydrochloride	4 (15.4)	1 (3.8)

FAS = full analysis set; IVA = ivacaftor; n = number of patients with event; PL = placebo; WHO = World Health Organization.
Source: ENVISION Clinical Study Report.[15]

TABLE 10: CHANGE IN PERCENTAGE PREDICTED FEV$_1$; FAS

Time Period	Treatment	N	Baseline Mean	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
					Difference	95% CI	P Value
KONNECTION							
Week 2	IVA	38	76.37	6.89	8.31	4.51 to 12.12	< 0.0001
	PL	37	79.34	−1.42			
Week 4	IVA	38	76.37	7.70	9.99	6.19 to 13.79	< 0.0001
	PL	37	79.34	−2.29			
Week 8	IVA	37	76.37	7.91	13.76	9.94 to 17.57	< 0.0001
	PL	37	79.34	−5.85			
Overall post-baseline through 8 weeks	IVA	38	76.37	7.49	10.67	7.26 to 14.10	< 0.0001
	PL	37	79.34	−3.19			
STRIVE							
Over 24 weeks	IVA	83	63.46	10.39	10.58	8.57 to 12.59	< 0.0001
	PL	78	63.67	−0.18			
Over 48 weeks	IVA	83	63.46	10.13	10.50	8.50 to 12.50	< 0.0001
	PL	78	63.67	−0.37			
ENVISION							
Over 24 weeks	IVA	26	84.73	12.58	12.45	6.56 to 18.34	< 0.0001
	PL	25	83.01	0.13			
Over 48 weeks	IVA	26	84.73	10.67	9.99	4.52 to 15.46	0.0006
	PL	25	83.01	0.68			

CI = confidence interval; FAS = full analysis set; FEV$_1$ = forced expiratory volume in one second; IVA = ivacaftor; LS = least square; N = number of patients; PL = placebo; vs. = versus.
Source: Clinical Study Reports for KONNECTION,[13] STRIVE,[14] and ENVISION.[15]

TABLE 11: CHANGE IN PERCENTAGE PREDICTED FEV$_1$ BY SUBGROUPS; FAS

Subgroup	Treatment Duration	Treatment	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
					Difference	95% CI	P Value
KONNECTION							
Age 6 to 11 y	8 weeks	IVA	▮	▮	▮	▮	▮
		PL	▮	▮			
Age 12 to 17 y		IVA	▮	▮	▮	▮	▮
		PL	▮	▮			
Age ≥ 18 y		IVA	▮	▮	▮	▮	▮
		PL	▮	▮			
FEV$_1$ < 70%		IVA	▮	▮	▮	▮	▮
		PL	▮	▮			
FEV$_1$ ≥ 70% to ≤ 90%		IVA	▮	▮	▮	▮	▮
		PL	▮	▮			

Subgroup	Treatment Duration	Treatment	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
					Difference	95% CI	P Value
FEV$_1$ > 90%		IVA	■	■	■	■	■
		PL	■	■			
STRIVE							
Age < 18 y	24 weeks	IVA	■	■	■	■	■
		PL	■	■			
Age ≥ 18 y		IVA	■	■	■	■	■
		PL	■	■			
Age < 18 y	48 weeks	IVA	■	■	11.4	■	0.0005
		PL	■	■			
Age ≥ 18 y		IVA	■	■	9.9	■	< 0.001
		PL	■	■			
FEV$_1$ < 70%	24 weeks	IVA	■	■	■	■	■
		PL	■	■			
FEV$_1$ ≥ 70%		IVA	■	■	■	■	■
		PL	■	■			
FEV$_1$ < 70%	48 weeks	IVA	■	■	10.6	■	< 0.001
		PL	■	■			
FEV$_1$ ≥ 70%		IVA	■	■	10.3	■	< 0.001
		PL	■	■			
ENVISION							
FEV$_1$ < 70%	24 weeks	IVA	■	NR	NR	NR	NR
		PL	■	NR			
FEV$_1$ ≥ 70% to ≤ 90%		IVA	■	■	■	■	■
		PL	■	■			
FEV$_1$ > 90%		IVA	10	■	6.9	−3.8 to 17.6	■
		PL	11	■			
FEV$_1$ < 70%	48 weeks	IVA	■	NR	NR	NR	NR
		PL	■	NR			
FEV$_1$ ≥ 70% to ≤ 90%		IVA	■	■	■	■	■
		PL	■	■			
FEV$_1$ > 90%		IVA	■	■	■	■	■
		PL	■	■			

CI = confidence interval; FAS = full analysis set; FEV$_1$ = forced expiratory volume in one second; IVA = ivacaftor; LS = least square; N = number of patients; PL = placebo; vs. = versus; y = year.
Note: Subgroup analysis was conducted only when number of patients with results in each treatment group was ≥ 5.
Source: Clinical Study Reports for KONNECTION,[13] STRIVE,[14] and ENVISION.[15]

TABLE 12: PULMONARY EXACERBATIONS; FULL ANALYSIS SET

Event Type	Treatment	Number of Patients With Event	Number of Events (Event Rate)	Treatment Effect (IVA vs. PL)		
				Rate Ratio	95% CI	*P* Value
KONNECTION (8 weeks; N = 38 for IVA and N = 37 for PL)						
All PE	IVA	■	■	■	■	■
	PL	■	■			
PE requiring hospitalization	IVA	■	■ (NR)	NR	NR	■
	PL	■	■ (NR)			
PE requiring IV antibiotic therapy	IVA	■	■ (NR)	NR	NR	■
	PL	■	■ (NR)			
STRIVE (N = 83 for IVA and N = 78 for PL)						
24 weeks						
All PE	IVA	■	■	■	■	■
	PL	■	■			
PE requiring hospitalization	IVA	■	■	■	■	■
	PL	■	■			
PE requiring IV antibiotic therapy	IVA	■	■	■	■	■
	PL	■	■			
48 weeks						
All PE	IVA	■	47 (0.59)	■	■	0.0003
	PL	■	99 (1.38)			
PE requiring hospitalization	IVA	■	21 (0.31)	■	■	0.1948
	PL	■	31 (0.49)			
PE requiring IV antibiotic therapy	IVA	■	28 (0.40)	■	■	0.0776
	PL	■	47 (0.71)			
ENVISION (N = 26 for IVA, N = 26 for PL)						
24 weeks						
All PE	IVA	■	■ (NR)	NR	NR	■
	PL	■	■ (NR)			
PE requiring hospitalization	IVA	■	■ (NR)	NR	NR	■
	PL	■	■ (NR)			
PE requiring IV antibiotic therapy	IVA	■	■ (NR)	NR	NR	■
	PL	■	■ (NR)			
48 weeks						
All PE	IVA	■	■ (NR)	NR	NR	■
	PL	■	■ (NR)			
PE requiring hospitalization	IVA	■	■ (NR)	NR	NR	■
	PL	■	■ (NR)			
PE requiring IV antibiotic therapy	IVA	■	■ (NR)	NR	NR	■
	PL	■	■ (NR)			

CI = confidence interval; FAS = full analysis set; IV = intravenous; IVA = ivacaftor; N = number of patients; NR = not reported;
PE = pulmonary exacerbations; PL = placebo; vs. = versus.
Note: Unit used for event rate was not mentioned.
Source: Clinical Study Reports for KONNECTION,[13] STRIVE,[14] and ENVISION.[15]

TABLE 13: CHANGE IN CFQ-R RESPIRATORY DOMAIN SCORE; FAS

Time Period	Treatment	Baseline Mean	N	Absolute Change From Baseline (LS Mean)	Treatment Effect (IVA vs. PL)		
					Difference	95% CI	*P* Value
KONNECTION							
Week 2	IVA	70.61	38	6.06	6.70	0.61 to 12.80	0.03
	PL	74.55	37	−0.64			
Week 4	IVA	70.61	38	9.45	9.37	3.27 to 15.47	0.0030
	PL	74.55	37	0.09			
Week 8	IVA	70.61	37	11.35	12.83	6.71 to 18.95	< 0.0001
	PL	74.55	37	−1.47			
Overall post-baseline	IVA	70.61	38	8.96	9.63	4.53 to 14.73	0.0004
	PL	74.55	37	−0.68			
STRIVE							
Overall post-baseline through 24 weeks	IVA	70.2	80	5.97	8.08	4.73 to 11.42	< 0.0001
	PL	69.0	70	−2.10			
Week 48	IVA	70.2	80	5.94	8.60	5.32 to 11.87	< 0.0001
	PL	69.0	70	−2.65			
ENVISION							
Week 24[a]	IVA	78.2	26	6.31	6.06	−1.41 to 13.53	0.1092
	PL	80.1	23	0.25			
Week 48[a]	IVA	78.2	26	6.06	5.06	−1.64 to 11.76	0.1354
	PL	80.1	22	1.00			
Week 24[b]	IVA	81.2	26	4.88	5.93	0.50 to 11.36	0.0330
	PL	80.8	23	−1.05			
Week 48[b]	IVA	81.2	26	3.69	4.88	−0.44 to 10.20	0.0713
	PL	80.8	22	−1.19			

CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval; FAS = full analysis set; IVA = ivacaftor; LS = least square; N = number of patients; PL = placebo; vs. = versus.
[a] Patient response.
[b] Parent or caregiver response.
Source: Clinical Study Report for KONNECTION,[13] STRIVE,[14] and ENVISION.[15]

TABLE 14: CHANGE IN CFQ-R RESPIRATORY DOMAIN SCORE BY SUBGROUP; FAS

Subgroup	Treatment Duration (Weeks)	Treatment	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
					Difference	95% CI	*P* Value
KONNECTION							
Age 6 to 11 y	8	IVA	▌	███	██	████	██
		PL	▌	██			
Age 12 to 17 y		IVA	█	██	██	███	██
		PL	▌	██			

Subgroup	Treatment Duration (Weeks)	Treatment	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
					Difference	95% CI	P Value
Age ≥ 18 y		IVA	■	■	■	■	■
		PL	■	■			
FEV$_1$ < 70%		IVA	■	■	■	■	■
		PL	■	■			
FEV$_1$ ≥ 70% to ≤ 90%		IVA	■	■	■	■	■
		PL	■	■			
FEV$_1$ > 90%		IVA	■	■	■	■	■
		PL	■	■			
STRIVE							
Age < 18 y	24	IVA	■	■	■	■	■
		PL	■	■			
Age ≥ 18 y		IVA	■	■	■	■	■
		PL	■	■			
Age < 18 y	48	IVA	■	■	■	■	■
		PL	■	■			
Age ≥ 18 y		IVA	■	■	■	■	■
		PL	■	■			
FEV$_1$ < 70%	24	IVA	■	■	■	■	■
		PL	■	■			
FEV$_1$ ≥ 70%		IVA	■	■	■	■	■
		PL	■	■			
FEV$_1$ < 70%	48	IVA	■	■	■	■	■
		PL	■	■			
FEV$_1$ ≥ 70%		IVA	■	■	■	■	■
		PL	■	■			
ENVISION							
FEV$_1$ < 70%	24	IVA	■	NR	NR	NR	NR
		PL	■	NR			
FEV$_1$ ≥ 70% to ≤ 90%		IVA	■	■	■	■	■
		PL	■	■			
FEV$_1$ > 90%		IVA	■	■	■	■	■
		PL	■	■			
FEV$_1$ < 70%	48	IVA	■	NR	NR	NR	NR
		PL	■	NR			
FEV$_1$ ≥ 70% to ≤ 90%		IVA	■	■	■	■	■
		PL	■	■			
FEV$_1$ > 90%		IVA	■	■	■	■	■
		PL	■	■			

CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval; FAS = full analysis set; FEV$_1$ = forced expiratory volume in one second; IVA = ivacaftor; LS = least square; N = number of patients; NR = not reported; PL = placebo; vs. = versus; y = year.
Source: Clinical Study Report for KONNECTION,[13] STRIVE,[14] and ENVISION.[15]

TABLE 15: KONNECTION (8 WEEKS): CHANGE IN CFQ-R NON-RESPIRATORY DOMAIN SCORE; FAS

Domain	Treatment	Baseline Mean	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
					Difference	95% CI	*P* Value
KONNECTION							
Physical	IVA	■	■	■	■	■	■
	PL	■	■	■			
Emotional	IVA	■	■	■	■	■	■
	PL	■	■	■			
Social	IVA	■	■	■	■	■	■
	PL	■	■	■			
Body	IVA	■	■	■	■	■	■
	PL	■	■	■			
Eating	IVA	■	■	■	■	■	■
	PL	■	■	■			
Treatment burden	IVA	■	■	■	■	■	■
	PL	■	■	■			
Digestive	IVA	■	■	■	■	■	■
	PL	■	■	■			

CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval; FAS = full analysis set; IVA = ivacaftor; LS = least square; N = number of patients; PL = placebo; vs. = versus.
Source: KONNECTION Clinical Study Report.[13]

TABLE 16: STRIVE: CHANGE IN CFQ-R NON-RESPIRATORY DOMAIN SCORE; FAS

CFQ-R Domain		Treatment	Baseline Mean	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
						Difference	95% CI	*P* Value
Physical	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
Emotion	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
Social	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
Body	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
Eating	24	IVA	■	■	■	■	■	■

CFQ-R Domain		Treatment	Baseline Mean	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
						Difference	95% CI	*P* Value
	weeks	PL	■	■	■			
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
Treatment burden	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
Digestive	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			

CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval; FAS = full analysis set; IVA = ivacaftor; LS = least square; N = number of patients; PL = placebo; vs. = versus.
Source: STRIVE.[14]

TABLE 17: ENVISION: CHANGE IN CFQ-R NON-RESPIRATORY DOMAIN SCORE; FAS; PATIENT RESPONSE

CFQ-R Domain		Treatment	Baseline Mean	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
						Difference	95% CI	*P* Value
Physical	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■		■	
	48 weeks	IVA	■		■	■	■	■
		PL	■		■		■	
Emotion	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■		■	
	48 weeks	IVA	■		■	■	■	■
		PL	■		■		■	
Social	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■		■	
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■		■	
Body	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■		■	
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■		■	
Eating	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■		■	
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■		■	
Treatment burden	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■		■	
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■		■	

CFQ-R Domain		Treatment	Baseline Mean	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
						Difference	95% CI	*P* Value
Digestive	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			

CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval; FAS = full analysis set; IVA = ivacaftor; LS = least square; N = number of patients; PL = placebo; vs. = versus.
Source: ENVISION Clinical Study Report.[15]

TABLE 18: ENVISION: CHANGE IN CFQ-R NON-RESPIRATORY DOMAIN SCORE; FAS; PARENT/CAREGIVER RESPONSE

CFQ-R Domain		Treatment	Baseline Mean	N	Overall Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
						Difference	95% CI	*P* Value
Physical	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
Vitality	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
Emotion	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
	48 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
Body	24 weeks	IVA	■	■	■	■	■	■
		PL	■	■	■			
	48 weeks	IVA				■	■	■
		PL						
Eating	24 weeks	IVA				■	■	■
		PL						
	48 weeks	IVA				■	■	■
		PL						
Treatment burden	24 weeks	IVA				■	■	■
		PL						
	48 weeks	IVA				■	■	■
		PL						
Health	24 weeks	IVA				■	■	■
		PL	■	■	■			
	48 weeks	IVA				■	■	■
		PL						
Weight	24 weeks	IVA	■		■	■	■	■

CFQ-R Domain		Treatment	Baseline Mean	N	Overall Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
						Difference	95% CI	*P* Value
		PL	███	█	███			
	48 weeks	IVA		█	███	██	██	██
		PL	███	█				
Digestive	24 weeks	IVA	███	█		█	██	██
		PL	███	█				
	48 weeks	IVA	███	█		█	█	█
		PL	███	█				
School	24 weeks	IVA	███	█		█	█	██
		PL	███	█				
	48 weeks	IVA	███	█		██	█	██
		PL	███	█				

CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval; FAS = full analysis set; IVA = ivacaftor; LS = least square; N = number of patients; PL = placebo; vs. = versus.
Source: ENVISION Clinical Study Report.[15]

TABLE 19: CHANGE IN EQ-5D INDEX SCORE; FAS

Study		Treatment	Baseline Mean	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
						Difference	(95% CI)	*P* Value
KONNECTION					NR			
STRIVE	24 weeks	IVA	0.93	82	0.004	0.019	(0.002 to 0.036)	0.0320
		PL	0.94	73	−0.015			
	48 weeks	IVA	0.93	82	0.002	0.018	(0.002 to 0.035)	0.0305
		PL	0.94	73	−0.017			
ENVISION					NR			

CI = confidence interval; EQ-5D = EuroQol questionnaire; FAS = full analysis set; IVA = ivacaftor; LS = least square; N = number of patients; NR = not reported; PL = placebo; vs. = versus.
Source: Clinical Study Report for KONNECTION,[13] STRIVE,[14] and ENVISION.[15]

TABLE 20: CHANGE IN BMI (KG/M^2); FAS

Time Period	Treatment	Baseline Mean	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
					Difference	95% CI	*P* Value
KONNECTION							
Week 8	IVA	22.24	38	0.68	0.66	0.34 to 0.99	< 0.0001
	PL	22.53	37	0.02			
STRIVE							
Week 24	IVA	21.75	80	0.92	0.94	0.62 to 1.26	< 0.0001
	PL	21.88	71	−0.02			
Week 48	IVA	21.75	77	0.91	0.93	0.48 to 1.38	< 0.0001
	PL	21.88	68	−0.02			

Time Period	Treatment	Baseline Mean	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
					Difference	95% CI	*P* Value
ENVISION							
Week 24	IVA	17.13	26	1.03	0.81	0.34 to 1.28	0.0008
	PL	16.83	26	0.22			
Week 48	IVA	17.13	26	1.34	1.09	0.51 to 1.67	0.0003
	PL	16.83	26	0.25			

BMI = body mass index; CI = confidence interval; FAS = full analysis set; IVA = ivacaftor; kg = kilogram; LS = least square; m^2 = square metre; N = number of patients; PL = placebo; vs. = versus.
Source: Clinical Study Report for KONNECTION,[13] STRIVE,[14] and ENVISION.[15]

TABLE 21: CHANGE IN BMI-FOR-AGE Z-SCORE; FAS

Time Period	Treatment	Baseline Mean	N[a]	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
					Difference	95% CI	*P* Value
KONNECTION							
Week 8	IVA	0.32	18	0.24	0.28	0.12 to 0.45	0.0010
	PL	0.49	17	−0.04			
STRIVE							
Week 24	IVA	−0.47	24	0.2989	0.34	0.14 to 0.54	0.0010
	PL	−0.56	23	−0.0441			
Week 48	IVA	−0.47	24	0.2491	0.33	0.00 to 0.65	0.0490
	PL	−0.56	23	−0.0765			
ENVISION							
Week 24	IVA	0.09	26	0.3046	0.34	0.16 to 0.51	0.0002
	PL	0.08	26	−0.0330			
Week 48	IVA	0.09	26	0.2788	0.45	0.26 to 0.65	< 0.0001
	PL	0.08	26	−0.1755			

BMI = body mass index; CI = confidence interval; FAS = full analysis set; IVA = ivacaftor; LS = least square; N = number of patients; PL = placebo; vs. = versus.
[a] BMI-for-age z-score was determined for patients up to 20 years of age in KONNECTION and STRIVE.
Source: Clinical Study Report for KONNECTION,[13] STRIVE,[14] and ENVISION.[15]

TABLE 22: CHANGE FROM BASELINE IN WEIGHT (KG); FAS

Time Period	Treatment	Baseline Mean	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
					Difference	95% CI	*P* Value
KONNECTION							
Week 8	IVA	57.93	38	2.01	1.67	0.71 to 2.63	0.0007
	PL	58.59	37	0.34			
STRIVE							
Week 24	IVA	61.70	83	2.95	2.75	1.76 to 3.74	< 0.0001
	PL	61.21	78	0.21			
Week 48	IVA	61.70	83	3.11	2.71	1.33 to 4.03	0.0001
	PL	61.21	78	0.40			
ENVISION							
Week 24	IVA	31.81	26	3.69	1.90	0.86 to 2.94	0.0004
	PL	30.04	26	1.79			
Week 48	IVA	31.81	26	5.85	2.77	1.31 to 4.23	0.0002
	PL	30.04	26	3.08			

CI = confidence interval; FAS = full analysis set; IVA = ivacaftor; kg = kilogram; LS = least square; N = number of patients;
PL = placebo; vs. = versus.
Source: Clinical Study Report for KONNECTION,[13] STRIVE,[14] and ENVISION.[15]

TABLE 23: CHANGE IN SWEAT CHLORIDE (MMOL/L); FAS

Time Period	Treatment	Baseline Mean	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
					Difference	95% CI	*P* Value
KONNECTION							
Week 2	IVA	93.37	33	−48.2025	−45.72	−53.95 to −37.48	< 0.0001
	PL	94.23	35	−2.4864			
Week 4	IVA	93.37	34	−52.97	−52.09	−60.29 to −43.89	< 0.0001
	PL	94.23	36	−0.88			
Week 8	IVA	93.37	36	−55.5863	−49.63	−57.80 to −41.47	< 0.0001
	PL	94.23	36	−5.953			
Overall post-baseline through 8 weeks	IVA	93.37	37	−52.25	−49.15	−56.86 to −41.43	< 0.0001
	PL	94.23	37	−3.11			
STRIVE							
Overall post-baseline through 24 weeks	IVA	100.35	78	−48.70	−47.93	−51.34 to −44.52	< 0.0001
	PL	100.13	74	−0.77			
Overall post-baseline through 48 weeks	IVA	100.35	78	−48.65	−48.07	−51.47 to −44.68	< 0.0001
	PL	100.13	74	−0.58			

Time Period	Treatment	Baseline Mean	N	Absolute Change From Baseline LS Mean	Treatment Effect (IVA vs. PL)		
					Difference	95% CI	P Value
ENVISION							
Overall post-baseline through 24 weeks	IVA	104.37	23	−55.53	−54.32	−61.83 to −46.82	< 0.0001
	PL	105.04	23	−1.21			
Overall post-baseline through 48 weeks	IVA	104.37	23	−56.04	−53.47	−60.92 to −46.02	< 0.0001
	PL	105.04	23	−2.57			

CI = confidence interval; FAS = full analysis set; IVA = ivacaftor; L = litre; LS = least square; mmol = millimole; N = number of patients; PL = placebo; vs. = versus.
Source: Clinical Study Report for KONNECTION,[13] STRIVE,[14] and ENVISION.[15]

TABLE 24: PROPORTION OF PATIENTS WITH DECREASE IN SWEAT CHLORIDE OF ≥ 30% OR < 30% FROM BASELINE

Study	Time Period	Decrease From Baseline in Sweat Chloride Level	Ivacaftor n (%)		Placebo n (%)	
KONNECTION (N = 39 IVA, 39 PL)	Week 8	≥ 30%		■		■
		< 30%				
STRIVE (N = 83 IVA, 78 PL)	Week 24	≥ 30%		■		■
		< 30%				
	Week 48	≥ 30%		■		■
		< 30%		■		■
ENVISION (N = 26 IVA, 26 PL)	Week 24	≥ 30%		■		■
		< 30%				
	Week 48	≥ 30%				
		< 30%				■

IVA = ivacaftor; n = number of patients with event; N = number of patients; PL = placebo.
Note: Proportions are based on number of patients with non-missing data at that time point.
Source: Manufacturer response to August 28, 2014 request for additional information.

TABLE 25: PROPORTION OF PATIENTS WITH SWEAT CHLORIDE OF < 60 MMOL/L OR ≥ 60 MMOL/L

Study	Time Period	Decrease From Baseline in Sweat Chloride Level (mmol/L)	Ivacaftor n (%)		Placebo n (%)	
STRIVE (N = 83 IVA, 78 PL)	Week 24	< 60		■		■
		≥ 60				
	Week 48	< 60		■		■
		≥ 60				
ENVISION (N = 26 IVA, 26 PL)	Week 24	< 60		■		■
		≥ 60				
	Week 48	< 60		■		■
		≥ 60				■

IVA = ivacaftor; L = litre; mmol = millimole; n = number of patients with event; N = number of patients; PL = placebo.
Note: Proportions are based on number of patients with non-missing data at that time point.
Source: Manufacturer response to August 28, 2014 request for additional information.

TABLE 26: EFFICACY OUTCOMES FOR SPECIFIC CFTR NON-G551D GATING MUTATIONS; FAS

Mutation (N)	Absolute Change in Per cent Predicted FEV$_1$ (%)	Absolute Change in BMI (kg/m^2)	Absolute Change in CFQ-R Respiratory Domain (Points)	Absolute Change in Sweat Chloride (mmol/L)
G178R (5)	8 (−1, 18)	0.85 (0.33, 1.46)	20.0 (5.6, 50.0)	−52.50 (−64.5, −35.0)
S549N (6)	11 (−2, 20)	0.79 (0.00, 1.91)	8.8 (−8.3, 27.8)	−74.25 (−92.5, −53.0)
S549R (4)	5 (−3, 13)	0.53 (0.33, 0.80)	6.9 (0.0, 11.1)	−60.67 (−70.5, −53.5)
G551S (2)	3[a]	0.16[b]	16.7[b]	−68.00 (−68.0, −68.0)
G970R (4)	3 (−1, 5)	0.48 (−0.38, 1.75)	1.4 (−16.7, 16.7)	−6.25 (−16.0, −2.0)
G1244E (5)	8 (−1, 18)	0.63 (0.34, 1.32)	3.3 (−27.8, 22.2)	−55.10 (−75.0, −34.0)
S1251N (8)	9 (−20, 21)	0.73 (0.08, 1.83)	23.3 (5.6, 50.0)	−54.38 (−84.0, −7.0)
S1255P (2)	3 (−1, 8)	1.62 (1.39, 1.84)	8.3 (5.6, 11.1)	−77.75 (−82.0, −73.5)
G1349D (2)	20 (3, 36)	1.15 (1.07, 1.22)	16.7 (−11.1, 44.4)	−80.25 (−81.5, −79.0)

BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire-Revised; FAS = full analysis set; FEV$_1$ = forced expiratory volume in one second; kg = kilogram; L = litre; m^2 = square metre; mmol = millimole; N = number of patients.
Note: Results are expressed as mean (minimum, maximum) and represent change from baseline for patients treated with ivacaftor.
[a] Reflects results from the 1 subject with the *G551S* mutation who had data at the 8-week time point.
Source: CADTH Common Drug Review Submission.[16]

TABLE 27: HARMS OCCURRING IN KONNECTION, 8 WEEKS; SAFETY SET

Outcome	IVAN (%)	PLN (%)
AE		
Patients with any AE	28 (73.7)	31 (83.8)
Most common AEs (≥ 10% of patients)		
Infective pulmonary exacerbation of CF	9 (23.7)	11 (29.7)
Cough	5 (13.2)	7 (18.9)
Oropharyngeal pain	1 (2.6)	4 (10.8)
Pyrexia	3 (7.9)	1 (2.7)
Fatigue	2 (5.3)	0 (0)
Abdominal pain	1 (2.6)	4 (10.8)
Headache	3 (7.9)	5 (13.5)
SAE, N (%)		
Patients with > 0 SAEs	4 (10.5)	8 (21.6)
Most common SAEs (> 2%)		
Infective pulmonary exacerbation of CF	2 (5.3)	2 (5.4)
Tonsillitis	0	1 (2.7)
Paranasal cyst	0	1 (2.7)
Pneumothorax	0	1 (2.7)
Distal ileal obstruction syndrome	1 (2.6)	1 (2.7)
Appendiceal mucocoele	0	1 (2.7)
Distal intestinal obstruction syndrome	0	1 (2.7)
Intussusception	0	1 (2.7)
Headache	1 (2.6)	0
Hepatic enzyme increased	0	1 (2.7)
Intervertebral disc protrusion	1 (2.6)	0
WDAE, N (%)		
WDAEs, N (%)	0	0

AE = adverse event; CF = cystic fibrosis; IVA = ivacaftor; N = number of patients; PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: KONNECTION Clinical Study Report.[13]

TABLE 28: HARMS OCCURRING IN STRIVE, 48 WEEKS; SAFETY SET

Outcome	IVA N (%)	PL N (%)
AE		
Patients with any AE	82 (98.8)	78 (100.0)
Most common AEs (≥ 10% of patients)		
CF lung exacerbations	34 (41.0)	50 (64.1)
Cough	27 (32.5)	33 (42.3)
Headache	19 (22.9)	13 (16.7)
Upper respiratory tract infection	19 (22.9)	12 (15.4)
Nasal congestion	17 (20.5)	12 (15.4)
Oropharyngeal pain	17 (20.5)	15 (19.2)
Abdominal pain	13 (15.7)	10 (12.8)
Nausea	13 (15.7)	9 (11.5)
Rash	12 (14.5)	4 (5.1)
Diarrhea	11 (13.3)	10 (12.8)
Dizziness	10 (12.0)	1 (1.3)
Nasopharyngitis	10 (12.0)	10 (12.8)
Pyrexia	10 (12.0)	9 (11.5)
Hemoptysis	9 (10.8)	17 (21.8)
Rales	9 (10.8)	8 (10.3)
Vomiting	9 (10.8)	10 (12.8)
PFT decreased	3 (3.6)	11 (14.1)
SAE, N (%)		
Patients with > 0 SAEs	20 (24.1)	33 (42.3)
Most common SAEs (> 2%)		
CF lung exacerbations	11 (13.3)	26 (33.3)
Hypoglycemia	2 (2.4)	0
Hemoptysis	1 (1.2)	4 (5.1)
WDAE, N (%)		
WDAEs, N (%)	1 (1.2)	4 (5.1)
Most common reasons (> 1%)		
ALT increased	0	1 (1.3)
Hepatic enzyme increased	1 (1.2)	0
Atrioventricular block	0	1 (1.3)
Panic attack	0	1 (1.3)
Respiratory failure	0	1 (1.3)

AE = adverse event; ALT = alanine aminotransferase; CF = cystic fibrosis; IVA = ivacaftor; N = number of patients; PL = placebo; PFT = pulmonary function test; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: STRIVE Clinical Study Report.[14]

TABLE 29: HARMS OCCURRING IN ENVISION, 48 WEEKS; SAFETY SET

Outcome	IVA N (%)	PL N (%)
AE		
Patients with any AE	26 (100.0)	25 (96.2)
Most common AEs (≥ 10% of patients)		
Cough	13 (50.0)	19 (73.1)
CF lung exacerbations	8 (30.8)	8 (30.8)
Headache	7 (26.9)	4 (15.4)
Oropharyngeal pain	7 (26.9)	4 (15.4)
Abdominal pain upper	6 (23.1)	5 (19.2)
Nasopharyngitis	6 (23.1)	2 (7.7)
Pyrexia	6 (23.1)	7 (26.9)
Upper respiratory tract infection	6 (23.1)	2 (7.7)
Nasal congestion	5 (19.2)	4 (15.4)
Abdominal pain	4 (15.4)	3 (11.5)
Otitis media	4 (15.4)	1 (3.8)
AST increased	3 (11.5)	2 (7.7)
Bronchitis	3 (11.5)	2 (7.7)
Diarrhea	3 (11.5)	0
Eosinophil count increased	3 (11.5)	1 (3.8)
Rhinorrhea	3 (11.5)	4 (15.4)
Wheezing	3 (11.5)	4 (15.4)
PFT decreased	2 (7.7)	4 (15.4)
Rales	2 (7.7)	4 (15.4)
ALT increased	2 (7.7)	3 (11.5)
Rash	2 (7.7)	3 (11.5)
Sinusitis	2 (7.7)	3 (11.5)
SAE, N (%)		
Patients with > 0 SAEs	5 (19.2)	6 (23.1)
Most common SAEs (> 2%)		
CF lung exacerbations	2 (7.7)	3 (11.5)
Abdominal pain	1 (3.8)	0
Conversion disorder	1 (3.8)	0
Hepatic enzyme increased	1 (3.8)	0
Muscle strain	1 (3.8)	0
Productive cough	1 (3.8)	1 (3.8)
Pyrexia	1 (3.8)	0
Adjustment disorder	0	1 (3.8)
Affective disorder	0	1 (3.8)
Anxiety	0	1 (3.8)
Constipation	0	1 (3.8)
Lung consolidation	0	1 (3.8)
Pseudomonas infection	0	1 (3.8)
PFT decreased	0	1 (3.8)

Outcome	IVA N (%)	PL N (%)
WDAE, N (%)		
WDAEs, N (%)	0	1 (3.8)
Most common reasons (> 1%)		
Adjustment disorder	0	1 (3.8)
Affective disorder	0	1 (3.8)
Anxiety	0	1 (3.8)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CF = cystic fibrosis; IVA = ivacaftor; N = number of patients; PL = placebo; PFT = pulmonary function test; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: ENVISION Clinical Study Report.[15]

TABLE 30: NOTABLE HARMS (HEPATIC RELATED) REPORTED IN KONNECTION

Outcome	IVA N (%)	PL N (%)
ALT increased	1 (2.6)	0
GGT increased	1 (2.6)	0
Hepatic enzyme increased	0	1 (2.7)

ALT = alanine aminotransferase; GGT = gamma-glutamyltransferase; IVA = ivacaftor; N = number of patients; PL = placebo.
Source: KONNECTION Clinical Study Report.[13]

TABLE 31: NOTABLE HARMS (HEPATIC RELATED) REPORTED IN STRIVE

Outcome	IVA N (%)	PL N (%)
ALP increased	3 (3.6)	3 (3.8)
ALT increased	5 (6.0)	5 (6.4)
AST increased	5 (6.0)	2 (2.6)
Blood bilirubin increased	1 (1.2)	2 (2.6)
Cytolytic hepatitis	1 (1.2)	0
GGT increased	2 (2.4)	3 (3.8)
Hepatic enzyme increased	4 (4.8)	3 (3.8)
Liver function test abnormal	0	1 (1.3)
Liver palpable subcostal	0	1 (1.3)
Transaminases increased	0	1 (1.3)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; IVA = ivacaftor; N = number of patients; PL = placebo.
Source: STRIVE Clinical Study Report.[14]

TABLE 32: NOTABLE HARMS (HEPATIC RELATED) REPORTED IN ENVISION

Outcome	IVA N (%)	PL N (%)
ALT increased	2 (7.7)	3 (11.5)
AST increased	3 (11.5)	2 (7.7)
GGT increased	0	1 (3.8)
Hepatic enzyme increased	1 (3.8)	0
Liver palpable subcostal	1 (3.8)	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; IVA = ivacaftor; N = number of patients; PL = placebo.
Source: ENVISION Clinical Study Report.[15]

TABLE 33: POST-HOC ANALYSIS OF PATIENTS FROM STRIVE AND ENVISION GROUPED BY FEV$_1$ RESPONSE TO IVACAFTOR OR PLACEBO

Outcome	FEV$_1$ Tertiles[a]					
	Lower: Ivacaftor: N = 37, FEV$_1$ ≤ 5.56 Placebo: N = 34, FEV$_1$ ≤ −2.65		Middle: Ivacaftor: N = 36, FEV$_1$ > 5.56 and ≤ 13.59 Placebo: N = 33, FEV$_1$ > −2.65 and ≤ 1.74		Upper: Ivacaftor: N = 36, FEV$_1$ > 13.59 Placebo: N = 33, FEV$_1$ > 1.74	
	Ivacaftor (Lower Tertile) vs. Placebo (Lower Tertile)	Ivacaftor (Lower Tertile) vs. Placebo (Overall — i.e., All Tertiles)	Ivacaftor (Middle Tertile) vs. Placebo (Middle Tertile)	Ivacaftor (Middle Tertile) vs. Placebo (Overall — i.e., All Tertiles)	Ivacaftor (Upper Tertile) vs. Placebo (Upper Tertile)	Ivacaftor (Upper Tertile) vs. placebo (Overall — i.e., All Tertiles)
Between-treatment difference, mean (95% CI), *P* value						
Days with pulmonary exacerbation	■	■	■	■	■	■
Change from baseline in CFQ-R (respiratory domain) score (points)	■	■	■	■	■	■
Change from baseline in body weight (kg)	■	■	■	■	■	■
Change from baseline in sweat chloride level (mmol/L)	■	■	■	■	■	■

CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval; FEV$_1$ = forced expiratory volume in one second; kg = kilogram; L = litre; mmol = millimole; N = number of patients; vs. = versus.
[a] Subgroups of patients were defined by tertiles with respect to FEV$_1$ response. Patients were assigned to a tertile (lower, middle, and upper) within treatment groups based on the absolute change from baseline in per cent predicted FEV$_1$ response through week 48. Treatment effects were compared within tertiles and with overall pooled placebo.
Source: Submission material.[16]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

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

Aim

To summarize the validity and minimal clinically important differences (MCID) of the following outcome measures:
- Forced Expiratory Volume in one second (FEV_1)
- Cystic Fibrosis Questionnaire-Revised (CFQ-R)
- European Quality of Life Scale (EQ-5D).

Findings

Forced Expiratory Volume in One Second

FEV_1 is the maximal amount of air forcefully exhaled in one second, expressed in litres.[63] The measured volume is converted to a percentage of predicted normal value, which is adjusted based on age, sex, and body composition.[63] FEV_1 is used in establishing 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 CF.[63,64]

FEV_1 is a commonly used end point for clinical trials of obstructive lung diseases including CF[48] and is the preferred end point in the European Medicines Agency (EMEA) guidance document on the development of therapeutic drugs for CF, based on the fact that the main pulmonary defect in CF is obstructive.[64] FEV_1 has been shown to relate to morbidity, disease progression, and mortality in CF making it a meaningful surrogate marker for survival.[48]

However, there are limitations with FEV_1:
- The manoeuvre required to assess FEV_1 is highly dependent on patient co-operation and effort:
  - The test (spirometry) should be repeated at least three times to ensure reproducibility.[63]
  - 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.[48,64]
  - FEV_1 can only be underestimated, never overestimated (exception: FEV_1 can be overestimated in people with some diseases — a softer blow can reduce the spasm or collapse of lung tissue to elevate the measure).

- FEV_1 decline is only meaningful over time and is subject to seasonal and environmental effects.[48]
- There are no published data on the clinically meaningful magnitude of change of FEV_1.[48]
- CF is a multi-organ disease and FEV_1 measures only lung health.[48]
- FEV_1 improvement has a ceiling effect for patients with mild lung impairment.[48]

The EMEA 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.[64]

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).[65] It consists of three modules: a QoL module containing both generic (physical functioning, energy, emotional, social limitations, role limitations) and disease-specific domains (body image, eating disturbances, treatment constraints); a symptoms module with three symptom scales (respiratory, digestive, and weight); and a health perception module. Items are summed to generate a domain score and standardized; scores range from 0 to 100, with higher scores indicating better QoL. The scales are designed to measure functioning during the two-week period prior to administration of the CFQ-R.[32]

The CFQ-R measures are well studied, several of which have evaluated the validity and reliability of the questionnaire.[66-68] Recently, Quittner et al.[66] examined the psychometric properties of the CFQ-R using data from the Epidemiologic Study of CF, a national US multi-centre longitudinal cohort study containing CFQ-R and health outcomes data from 7,330 patients aged six to 70 years. They reported adequate internal consistency (Cronbach alpha ≥ 0.70) for most domains and scales on each of the three versions. The CFQ was sensitive to changes in QoL associated with increasing disease severity (based on pulmonary function, FEV_1); this analysis was limited, however, since the CFQ-C had less variability in disease severity as few school-age children had a FEV_1 < 70% predicted. Quittner et al.[66] also reported fair to moderate agreement between the child-parent versions on all scales (intraclass correlation coefficient range 0.26 to 0.56); however, stronger agreement was found on domains that measured more observable signs and symptoms, such as physical functioning, eating problems, and respiratory symptoms. There was fair to moderate convergence between CFQ-R scales and health outcomes, including FEV_1 per cent predicted (correlation range, 0.25 to 0.51), number of pulmonary exacerbations treated with IV antibiotics (range –0.23 to –0.35), and body mass index (BMI) (range 0.22 to 0.44). The strongest correlations were demonstrated for the physical functioning and respiratory domains with FEV_1 per cent predicted (range 0.33 to 0.51 and 0.32 to 0.42, respectively) and for the weight scale and BMI (r = 0.42 and 0.44 on the CFQ-P and CFQ-14, respectively). Overall, the correlations were lower for the CFQ-C and CFQ-P versus the CFQ-14. Test-retest reliability was assessed previously (repeat administration over 14 days) and intraclass correlation coefficients were estimated to range from 0.45 to 0.90 on all scales.[67]

A previous study[67] also showed the CFQ-R correlated well with the SF-36. Correlations were high (r = 0.42 to 0.57) between similar dimensions of the CFQ and SF-36 (physical, health perceptions/general health, vitality, role/role physical, emotional functioning/mental health, and social) and low (r = 0.19 to 0.42) between scales not expected to be related (digestion and role scales of the CFQ and general health and mental health scales of the SF-36).

The MCID was estimated using the CFQ-R-respiratory symptom scale in two study populations: one with patients with stable CF and chronic *P. aeruginosa* airway infection; the other with patients with exacerbation of CF and chronic *P. aeruginosa* airway infection.[32] Both anchor-based and distribution methods were used. The MCID, or the smallest change a patient could detect in terms of changes in respiratory symptoms, for patients with stable disease was determined to be 4.0 and for patients with exacerbation was 8.5.[32] The difference in MCID estimates likely reflects differences in patient disease status (exacerbation versus stable).

The main limitations of the CFQ-R are ceiling effects for certain scales (notably the eating problems scale), potential difficulty for patients to understand some of the items (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 (response choices such as "somewhat" versus "a little").[48,66]

European Quality of Life Scale

The EQ-5D[50,51] is a generic QoL instrument that has been applied to a wide range of health conditions and treatments including CF. The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[50,51] 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 which best represents their own health on that day. Hence, the EQ-5D produces three types of data for each respondent:

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

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

The MCID for the EQ-5D ranges from 0.033 to 0.074.[52] The validity and MCID of the EQ-5D have not been formally assessed in CF.

Conclusion

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

APPENDIX 6: SUMMARY OF OTHER STUDIES

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

Aim
To summarize data from extension studies of randomized controlled trials (RCTs) of ivacaftor for cystic fibrosis (CF).

Findings
KONNECTION (part 2)[43]

Part 2 of KONNECTION (Study 111)[43] was a non-randomized, single-arm, 16-week, open-label extension period immediately following part 1. Patients with CF who had at least one allele of a non-G551D CF transmembrane conductance regulator (CFTR) gating mutation continued to receive 150 mg every 12 hours in addition to their usual, prescribed CF therapy (with the exception of hypertonic saline). The primary outcome measure in part 2 was absolute change from baseline in per cent predicted FEV_1 through 24 weeks of ivacaftor treatment (eight weeks in part 1, plus 16 weeks in part 2). The secondary outcomes in part 2 included number of patients experiencing pulmonary exacerbation, absolute change from baseline in body mass index (BMI), sweat chloride, and the respiratory domain score of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) through 24 weeks of treatment. Safety and tolerability were also measured through 24 weeks of treatment. Descriptive summary statistics were provided by treatment sequence in part 1. A total of 36 patients (18 from each treatment sequence group) from part 1 completed the open-label extension.

Between-treatment statistical testing was not performed for efficacy and safety outcomes. Mean absolute changes from baseline in per cent predicted FEV_1, CFQ-R respiratory domain score, BMI, and sweat chloride are presented in Table 34; improvements through 24 weeks in part 2 were sustained or exceeded those observed over the initial eight weeks of treatment.

As seen in Table 35, AEs were reported in most patients (83.3% in the placebo-ivacaftor group and 83.3% ivacaftor-placebo group from part 1), and were predominantly respiratory-related (exacerbations and cough). The incidence of serious adverse events (SAEs) in part 2 was 16.7% among the ivacaftor-placebo group. There were no SAEs among patients in the placebo-ivacaftor group, and no WDAE. With the exception of headaches, there did not appear to be an overall increasing trend with increased exposure of ivacaftor. There were no deaths in KONNECTION.

TABLE 34: SUMMARY OF KEY EFFICACY OUTCOMES FROM KONNECTION PART 2

Outcome	KONNECTION Part 1 (at 8 Weeks)		KONNECTION Part 2 Open-Label Extension	
	IVA (n = 38)	PL (n = 37)	IVA-PB[a] (n = 18)	PL-IVA[a] (n = 18)
Mean (SD) absolute change from baseline FEV_1 % predicted	7.91(NR)	−5.85 (NR)	10.44 (13.24)	13.53 (10.18)
Number of patients with PE, n (%)	9 (23.7)	8 (21.6)	3 (16.7)	3 (16.7)
PE requiring hospitalization (number of patients with event), n (%)	2 (5.3)	5 (13.5)	2 (11.1)	2 (11.1)
PE requiring IV antibiotic therapy, (number of	3 (7.9)	5 (13.5)	2 (11.1)	1 (5.6)

Outcome	KONNECTION Part 1 (at 8 Weeks)		KONNECTION Part 2 Open-Label Extension	
	IVA (n = 38)	PL (n = 37)	IVA-PB[a] (n = 18)	PL-IVA[a] (n = 18)
patients with event) n (%)				
Mean (SD) absolute change from baseline (points) CFQ-R respiratory domain	11.35 (NR)	−1.47 (NR)	9.10 (16.72)	11.42 (13.60)
Mean (SD) absolute change from baseline in BMI (kg/m2)	0.68 (NR)	0.02 (NR)	0.437 (1.09)	1.26 (0.76)
Mean (SD) absolute change from baseline in sweat chloride	−55.59 (NR)	−5.95 (NR)	−43.03 (33.48)	−59.24 (32.57)

CFQ-R = Cystic Fibrosis Questionnaire-Revised; BMI = body mass index; FEV_1 = forced expiratory volume in one second; IV = intravenous; IVA = ivacaftor; kg = kilogram; m^2 = square metre; n = number of patients with event; N = number of patients; NR = not reported; PL = placebo; PE = pulmonary exacerbation; SD = standard deviation.
[a] Randomized sequence in part 1.
Source: KONNECTION Clinical Study Report.[43]

TABLE 35: SUMMARY OF KEY HARMS OUTCOMES FROM KONNECTION PART 2

Adverse Events, n (%)	KONNECTION Part 1 (Through 8 Weeks)[a]		KONNECTION Part 2 Open-label Extension[b]	
	IVA (N = 38)	PL (n = 37)	PL-IVA[c] (n = 18)	IVA-PL[c] (n = 18)
AEs	28 (73.7)	31 (83.8)	15 (83.3)	15 (83.3)
CF lung exacerbations	9 (23.7)	11 (29.7)	3 (16.7)	3 (16.7)
Cough	5 (13.2)	7 (18.9)	3 (16.7)	2 (11.1)
Upper respiratory tract infection	1 (2.6)	2 (5.4)	1 (5.6)	2 (11.1)
Headache	3 (7.9)	5 (13.5)	0	4 (22.2)
Oropharyngeal pain	1 (2.6)	3 (8.1)	2 (11.1)	1 (5.6)
Abdominal pain	1 (2.6)	4 (10.8)	2 (11.1)	1 (5.6)
Pyrexia	3 (7.9)	1 (2.7)	0	2 (11.1)
SAEs[d]	4 (10.5)	7 (18.9)	0	3 (16.7)
CF lung exacerbations	2 (5.3)	6 (16.2)	0	2 (11.1)
Distal intestinal obstruction syndrome	1 (2.6)	0	0	1 (5.6)
Dehydration	0	0	0	1 (5.6)
Convulsion	0	0	0	1 (5.6)
Dizziness	0	0	0	1 (5.6)
Intervertebral disc protrusion	1 (2.6)	0	0	0
Appendiceal mucocele	0	1 (2.7)	0	0
Intussusception	0	1 (2.7)	0	0
Paranasal cyst	0	1 (2.7)	0	0
Pneumothorax	0	1 (2.7)	0	0
WDAEs	0	0	0	0

AE = adverse event; CF = cystic fibrosis; IVA = ivacaftor; n = number of patients with event; N = number of patients; NR = not reported; PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] In ≥ 3% of patients.
[b] In ≥ 2 patients.
[c] Randomized sequence in part 1.
[d] Patients may have had more than one serious adverse event.
Source: KONNECTION Clinical Study Report.[43]

PERSIST[69]

PERSIST (Study 105),[69] a phase 3, open-label, extension study, was identified presenting long-term follow-up efficacy and safety data on ivacaftor for the treatment of CF. All patients who enrolled in and completed STRIVE and ENVISION were eligible for inclusion in PERSIST; those randomized to the placebo group in STRIVE or ENVISION crossed over to ivacaftor in the PERSIST study. In total, 192 patients were enrolled (144 of 145 who completed STRIVE and 45 of 48 who completed ENVISION). At the time of the interim analysis (presented here), 128 patients (88.9%) from STRIVE completed at least 96 weeks treatment in PERSIST (72 originally randomized to ivacaftor and 56 to placebo), while 45 patients enrolled from ENVISION completed at least 96 weeks of PERSIST (24 originally randomized to ivacaftor and 21 to placebo). Patients who received placebo in the previous study were referred to as the "placebo-ivacaftor" group, while those who remained on ivacaftor throughout both studies were referred to as the "ivacaftor-ivacaftor" group. Sixteen patients from STRIVE discontinued treatment (n = 2 adverse event, n = 1 pregnancy, n = 3 noncompliance, n = 5 withdrawn consent, n = 1 prohibited medication use, and n = 2 death [unrelated]). Three patients from ENVISION discontinued treatment (n = 1 adverse event, n = 1 withdrew consent, and n = 1 noncompliance).

The majority of included patients were Caucasian (95%), with a mean age of 23 years at baseline (range 7 years to 54 years). The proportion of male and female patients was similar (47% versus 53%). There were differences in baseline weight (59 kg for ivacaftor-ivacaftor group versus 54 kg for placebo-ivacaftor group) and per cent predicted FEV_1 before the first dose in PERSIST (78% for ivacaftor-ivacaftor group vs 68% for placebo-ivacaftor group).

Baseline was defined as the most recent measurement before intake of the first dose of the study drug in either STRIVE or ENVISION. Absolute changes from baseline in per cent predicted FEV_1 are presented in Table 36. Improvements in per cent predicted FEV1 from the previous studies (STRIVE and ENVISION) were sustained through the additional 96 weeks in PERSIST among the ivacaftor-ivacaftor group, while improvements in per cent predicted FEV1 in PERSIST among the placebo-ivacaftor group were similar to those observed in the ivacaftor groups of STRIVE and ENVISION. The absolute changes from baseline in EQ-5D index score (only measured in STRIVE patients) were generally similar across the STRIVE and PERSIST studies (Table 36). Absolute changes from baseline in CFQ-R respiratory domain score are presented in Table 36. At week 144, improvements in CFQ-R respiratory were generally sustained among the ivacaftor-ivacaftor group from STRIVE. There was an improvement in CFQ-R respiratory domain score for the placebo-ivacaftor groups from both STRIVE and ENVISION. Absolute changes from baseline in body weight (kg) are presented in Table 36. Interpretation of changes in body weight are complicated by normal maturation, particularly in ENVISION that exclusively enrolled children. However, for patients who received placebo for 48 weeks in STRIVE, the subsequent 48 weeks of ivacaftor treatment in PERSIST (to week 96) produced noticeable weight gains (Table 36).

The safety profile for ivacaftor observed during PERSIST was generally consistent with that observed in STRIVE and ENVISION. With the exception of CF lung exacerbations and hemoptysis among STRIVE patients, there did not appear to be an overall increasing trend with increased exposure from the original RCTs. Most patients (92.2% from STRIVE and 92.3% from ENVISION) had at least one adverse event at the time of the interim analysis of PERSIST (Table 37) and were predominantly respiratory-related (exacerbations, cough, and upper respiratory tract infection). As seen in Table 37, the incidence of SAEs among patients from STRIVE was generally similar for all ivacaftor treatment periods (ranging from 19% to 25%) and lower compared with placebo (42%). The incidence of SAEs among patients from ENVISION was generally similar for all ivacaftor treatment periods (ranging from 19% to 23%) and placebo (23%). The most common serious adverse event among patients from both STRIVE and

ENVISION was CF lung exacerbations. WDAEs were rare as only one patient (2.1%) treated with ivacaftor prematurely withdrew from PERSIST due to an adverse event. Two deaths occurred during PERSIST, both non-treatment-related, as one patient died due to respiratory failure, and the other who committed suicide.

TABLE 36: SUMMARY OF KEY EFFICACY OUTCOMES FROM THE PERSIST EXTENSION STUDY

Efficacy Outcome	STRIVE			ENVISION		
	Week 48 (STRIVE)	Week 96 (PERSIST)	Week 144 (PERSIST)	Week 48 (ENVISION)	Week 96 (PERSIST)	Week 144 (PERSIST)
Mean (SD) absolute change from baseline FEV$_1$ % predicted						
IVA-IVA	9.4 (8.3) n = 77	9.1 (10.8)[a] n = 74	9.4 (10.8)[b] n = 72	10.2 (15.7) n = 26	9.0 (15.2)[a] n = 25	10.3 (12.4)[b] n = 25
PL-IVA	−1.2 (7.8) n = 67	9.4 (8.5) n = 63	9.5 (11.2) n = 55	−0.6 (10.1) n = 22	8.8 (12.5) n = 22	10.5 (11.5) n = 21
Number of patients with pulmonary exacerbations, n (%)						
IVA-IVA	▮	▮	▮	▮	▮	▮
PL-IVA	▮	▮	▮	▮	▮	▮
PE requiring hospitalization (number of patients with event)**, n (%)**						
IVA-IVA	▮	▮	▮	▮	▮	▮
PL-IVA	▮	▮	▮	▮	▮	▮
PE requiring IV antibiotic therapy (number of patients with event)**, n (%)**						
IVA-IVA	▮	▮	▮	▮	▮	▮
PL-IVA	▮	▮	▮	▮	▮	▮
EQ-5D index score						
IVA-IVA Baseline, mean (SD)	▮			NR		
Mean (SD) absolute change from baseline	▮	▮	▮	NR		
PL-IVA Baseline, mean (SD)	▮			NR		
Mean (SD) absolute change from baseline	▮	▮	▮	NR		
CFQ-R respiratory (points)						
IVA-IVA Baseline, mean (SD)	▮			▮		
Mean (SD) absolute change from baseline	6.4 (16.8) n = 74	4.9 (20.0)[a] n = 71	6.8 (19.6)[b] n = 69	7.4 (17.4) n = 26	4.3 (24.1)[a] n = 25	10.6 (18.9)[b] n = 25
PL-IVA Baseline, mean (SD)	▮			▮		
Mean (SD) absolute change from baseline	−3.6 (14.1) n = 61	8.6 (17.2) n = 64	9.8 (16.2) n = 56	0.8 (18.4) n = 22	4.2 (14.5) n = 22	10.8 (12.8) n = 21

Efficacy Outcome	STRIVE			ENVISION		
	Week 48 (STRIVE)	Week 96 (PERSIST)	Week 144 (PERSIST)	Week 48 (ENVISION)	Week 96 (PERSIST)	Week 144 (PERSIST)
Body weight (kg)						
IVA-IVA Baseline, mean (SD)	▮▮▮▮▮			▮▮▮▮▮		
Mean (SD) absolute change from baseline	3.4 (4.9) n = 77	3.7 (6.5)[a] n = 74	4.1 (7.1)[b] n = 72	6.1 (2.9) n = 26	10.5 (4.7)[a] n = 25	14.8 (5.7)[b] n = 25
PL-IVA Baseline, mean (SD)	▮▮▮▮▮			▮▮▮▮▮		
Mean (SD) absolute change from baseline	0.3 (2.7) n = 67	3.4 (3.7) n = 64	3.0 (4.7) n = 55	2.9 (1.8) n = 22	6.0 (−2.9) n = 22	10.1 (4.1) n = 21

CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire-Revised; FEV$_1$ = forced expiratory volume in one second;

IV = intravenous; IVA = ivacaftor; kg = kilogram; n = number of patients with event; N = number of patients; NR = not reported;

PL = placebo; PE = pulmonary embolism; SD = standard deviation.

[a] 96 weeks of cumulative ivacaftor exposure.

[b] 144 weeks of cumulative ivacaftor exposure.

Source: PERSIST Clinical Study Report.[69]

TABLE 37: SUMMARY OF KEY HARMS OUTCOMES FROM THE PERSIST EXTENSION STUDY

Adverse Events, n (%)	STRIVE[a]				ENVISION[b]			
	IVA			PL	IVA			PL
	Total Weeks of Exposure							
	< 48 (STRIVE) (n = 144)	48 to 96 (PERSIST) (n = 144)	96 to 144 (PERSIST) (n = 77)	< 48 (STRIVE) (n = 67)	< 48 (ENVISION) (n = 48)	48 to 96 (PERSIST) (n = 48)	96 to 144 (PERSIST) (n = 26)	< 48 (ENVISION) (n = 22)
AEs	138 (95.8)	136 (94.4)	71 (92.2)	67 (100.0)	46 (95.8)	45 (93.8)	24 (92.3)	22 (100.0)
CF lung exacerbations	55 (38.2)	72 (50.0)	40 (51.9)	45 (67.2)	13 (27.1)	9 (18.8)	6 (23.1)	8 (36.4)
Cough	45 (31.3)	34 (23.6)	16 (20.8)	29 (43.3)	19 (39.6)	14 (29.2)	11 (42.3)	17 (77.3)
Upper respiratory tract infection	28 (19.4)	24 (16.7)	22 (28.6)	12 (17.9)	12 (25.0)	7 (14.6)	8 (30.8)	2 (9.1)
Nasal congestion	22 (15.3)	12 (8.3)	2 (2.6)	10 (14.9)	6 (12.5)	4 (8.3)	2 (7.7)	4 (18.2)
Headache	25 (17.4)	16 (11.1)	12 (15.6)	11 (16.4)	10 (20.8)	5 (10.4)	5 (19.2)	4 (18.2)
Oropharyngeal pain	24 (16.7)	16 (11.1)	7 (9.1)	15 (22.4)	11 (22.9)	4 (8.3)	4 (15.4)	4 (18.2)
Hemoptysis	11 (7.6)	16 (11.1)	11 (14.3)	15 (22.4)	NR			
Abdominal pain	18 (12.5)	8 (5.6)	2 (2.6)	8 (11.9)	8 (16.7)	6 (12.5)	3 (11.5)	5 (22.7)
Diarrhea	16 (11.1)	8 (5.6)	0	9 (13.4)	3 (6.3)	3 (6.3)	3 (11.5)	0
Nasopharyngitis	17 (11.8)	11 (7.6)	7 (9.1)	9 (13.4)	9 (18.8)	6 (12.5)	4 (15.4)	2 (9.1)
Pyrexia	13 (9.0)	11 (7.6)	7 (9.1)	7 (10.4)	11 (22.9)	6 (12.5)	2 (7.7)	7 (31.8)
Vomiting	12 (8.3)	7 (4.9)	1 (1.3)	8 (11.9)	3 (6.3)	5 (10.4)	1 (3.8)	7 (31.8)
SAEs (≥ 2 patients)	27 (18.8)	33 (22.9)	19 (24.7)	28 (41.8)	8 (16.7)	9 (18.8)	6 (23.1)	5 (22.7)
CF lung exacerbations	14 (9.7)	22 (15.3)	13 (16.9)	24 (35.8)	4 (8.3)	4 (8.3)	2 (7.7)	3 (13.6)
Hemoptysis	2 (1.4)	4 (2.8)	2 (2.6)	4 (6.0)	NR			
Distal intestinal obstruction syndrome	1 (0.7)	2 (1.4)	0	0	NR			
WDAEs	0	0	0	0	0	1 (2.1)	0	0

AE = adverse event; CF = cystic fibrosis; IVA = ivacaftor; n = number of patients with event; N = number of patients; NR = not reported; PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] In 5% of patients.
[b] In 10% of patients.
Source: PERSIST Clinical Study Report.[69]

Limitations

The primary limitations in both KONNECTION part 2 and PERSIST are the lack of an adequate control group and open-label design. Efficacy results, specifically self-reported health-related QoL, should be interpreted with caution given the open-label design and patients' awareness of treatment.

Conclusion

KONNECTION part 2 was a 16-week open-label period that enrolled 36 patients with CF who had at least one allele of a non-G551D CFTR gating mutation from the randomized crossover period in part 1. Overall, the efficacy results through 24 weeks in part 2 were supportive of those observed over eight weeks of treatment in part 1. There were no new safety concerns with extended use of ivacaftor in part 2. Treatment with ivacaftor led to lower incidences of serious and non-SAEs when compared with placebo. PERSIST is an open-label, extension study that enrolled patients who completed STRIVE (n = 144) and ENVISION (n = 48). Sixty-seven patients from the original STRIVE placebo group crossed over to treatment with ivacaftor at the start of PERSIST, while 22 patients from the ENVISION placebo group crossed over to ivacaftor. Improvements in FEV_1 per cent predicted, CFQ-R respiratory domain, and body weight among patients treated with ivacaftor in STRIVE and ENVISION were sustained during PERSIST. The overall safety profile observed during PERSIST was generally consistent with that seen during STRIVE and ENVISION. Limitations of these open-label observational findings largely stem from the lack of a comparator group. Therefore, the extension data are suggestive of durability of response to ivacaftor, but they lack sufficient rigour to conclude this with confidence**.**

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