Common Drug Review
Clinical Review Report

June 2016

Drug	Ivacaftor (Kalydeco)
Indication	Treatment of cystic fibrosis in patients 18 years of age and older with a R117H mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene
NOC	March 13, 2015
Dosage Form	Tablet 150 mg
Listing Request	As per indication
Manufacturer	Vertex Pharmaceuticals Inc.

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

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ABBREVIATIONS

BMI	body mass index
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CF	cystic fibrosis
CF Canada	Cystic Fibrosis Canada
CFQ-14	Cystic Fibrosis Questionnaire – for individuals aged 14 years or older
CFQ-C	Cystic Fibrosis Questionnaire – for children aged six to 13 years
CFQ-P	Cystic Fibrosis Questionnaire – for parents who serve as a proxy for their child
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
FAS	full analysis set
FEV_1	forced expiratory volume in one second
MCID	minimal clinically important difference
MMRM	mixed effects model repeated measurements
$ppFEV_1$	per cent predicted forced expiratory volume in one second
PCR	polymerase chain reaction
RCT	randomized controlled trial
SD	standard deviation
SE	standard error

EXECUTIVE SUMMARY

Introduction

Cystic fibrosis (CF), an autosomal recessive condition, is the most common fatal genetic disease affecting children and young adults in Canada.[1,2] It is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, located on chromosome 7, which encodes a chloride channel that regulates ion and fluid transport across cell membranes.[1,2] When CFTR is dysfunctional, secretions become tenacious and sticky, resulting in pathology in multiple organs, including the lungs, large and small intestine, pancreatic and bile ducts, and vas deferens.[1] The R117H mutation is a less common CFTR variant that is present in approximately 3% of CF patients.[3,4] The clinical course for patients with the R117H mutation is variable, ranging from asymptomatic to classic CF.[3,5] It is difficult to predict the pulmonary disease course, as other factors, such as environmental and modifier genes, also influence the CF phenotype.[1,5] In symptomatic R117H CF patients, pulmonary disease is progressive and associated with premature mortality.[6]

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. This results in improved functioning of multiple organs; most notably, the lungs and gastrointestinal tract. Ivacaftor has a Health Canada indication for the treatment of CF in patients aged 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, and in patients aged 18 years and older with an R117H mutation in the CFTR gene. The Health Canada–recommended dose for adults is 150 mg every 12 hours with fat-containing food. Ivacaftor is available as 150 mg oral tablets.

Ivacaftor was reviewed previously by the CADTH Canadian Drug Expert Committee (CDEC) and was recommended for listing, at a substantial reduction in price, for the treatment of CF patients aged six years and older with G551D or non-G551D gating mutations (G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R).

Indication under review
Treatment of cystic fibrosis in patients 18 years of age and older with a R117H mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene
Listing criteria requested by sponsor
As per indication

The objectives of this report were to perform a systematic review of the beneficial and harmful effects of ivacaftor 150 mg tablet for the treatment of cystic fibrosis in patients aged 18 years or older with a R117H mutation of the CFTR gene.

Results and Interpretation

Included Studies

One randomized, double-blind study (KONDUCT) met the inclusion criteria for this review. The safety and efficacy of 24 weeks of ivacaftor (150 mg every 12 hours) was compared with placebo in patients aged six years or older with confirmed CF and the R117H mutation on at least one CFTR allele (N = 69, including 50 adults). The primary outcome was the change from baseline in per cent predicted forced

expiratory volume in one second ($ppFEV_1$) and secondary outcomes included pulmonary exacerbations, respiratory symptoms, body mass index (BMI), and sweat chloride levels. Randomization was stratified by age group (six to 11, 12 to 17, and ≥ 18 years), and $ppFEV_1$ (< 70, ≥ 70 to ≤ 90, and > 90). The trial was terminated early; as a result, four patients in each group did not complete 24 weeks of treatment. No justification was provided for early termination. However, sensitivity analysis with and without data from these eight patients did not alter study conclusions.

Key limitations of the trial were the small sample size and multiple testing of secondary outcomes without implementation of statistical procedures to avoid inflation of type I error. With respect to external validity, the clinical expert consulted for this review considered that patients enrolled in KONDUCT were largely representative of patients with the R117H mutation and pulmonary disease observed in clinical practice. However, it should be noted that some enrolled patients with a variant of the R117H mutation — i.e., R117H-7T — likely would not have met the diagnostic criteria for CF. This variant is not in itself considered disease-causing, and the CF diagnostic criteria for patients with this variant require a sweat chloride level exceeding 60 mmol/L. The mean baseline sweat chloride level among the 10 adults with the 7T variant was less than 60 mmol/L. Inclusion in the trial of patients who did not meet the diagnostic criteria for CF may have attenuated the apparent efficacy of ivacaftor versus placebo.

Efficacy

In the KONDUCT trial, ivacaftor was not associated with a statistically significant increase in $ppFEV_1$, relative to placebo for the overall trial population of patients with CF and the R117H mutation. Similarly, no statistically significant differences were found in the time to first pulmonary exacerbation, rate of exacerbations or change in BMI. However, ivacaftor was associated with statistically and clinically significant improvement in respiratory symptoms as measured by Cystic Fibrosis Questionnaire – Revised (CFQ-R) respiratory domain. Sweat chloride levels were also statistically significantly reduced, although the clinical relevance of treatment-related changes in sweat chloride levels is not known.

In the pre-specified subgroup analyses by age, adults treated with ivacaftor showed a statistically significant increase in $ppFEV_1$ versus placebo of 5% (95% confidence interval [CI] 1.1% to 8.8%, $P = 0.01$). Thirteen patients (54%) in the ivacaftor group achieved ≥ 5% absolute increase in $ppFEV_1$ compared with four patients (15%) in the placebo group. Adults who received ivacaftor also reported a clinically important improvement in respiratory symptoms, based on CFQ-R respiratory symptom domain scores (least-squares mean difference in score: 12.6; 95% CI, 5.0 to 20.3; $P = 0.002$; minimal clinically important difference [MCID], 4), but there were no significant differences in the time to first pulmonary exacerbation.

The treatment effects observed in the KONDUCT trial were smaller in magnitude than those observed in ivacaftor clinical trials that enrolled patients with a G551D or non-G551D gating mutation.[7-9] However, the patients enrolled in KONDUCT represent a different CF population that has highly variable and generally less severe CF disease. Although the study was not able to demonstrate an impact on exacerbations, these findings should be interpreted with caution considering the small sample size and relatively low event rates for this outcome. Decreasing exacerbations is an important outcome to patients and, given the limited data available in the trial, the clinical value of the drug for this important outcome is unclear. Moreover, ivacaftor was studied as an add-on to a stable regimen of CF medications and there is no evidence to suggest that ivacaftor may reduce overall treatment burden, which patients with CF report as a major concern.

Harms

No patients discontinued therapy due to adverse events and no deaths were reported in the 24-week KONDUCT trial. Ten patients reported serious adverse events during the KONDUCT trial (placebo: six [17%]; ivacaftor: four [12%]). Pulmonary exacerbation was the most frequently reported serious adverse event. No additional safety signals were identified in the first 12-week interim analysis of the open-label extension study.

Similar to the other gating mutation trials,[7-9] numerically more patients in the ivacaftor group reported oropharyngeal pain, nasal congestion, or abdominal pain, than placebo. No clear pattern of elevated liver function tests and no other liver-related adverse events were noted in the KONDUCT study. Considering the limited sample size and short duration of the study, additional data are needed to determine the long-term safety of ivacaftor.

Potential Place in Therapy[1]

While the clinical course is more variable compared with patients who carry two copies of CF mutations that confer no or minimal CFTR function (e.g., F508del, G551D, G542X), the majority of patients with CF and the R117H mutation will have progressive lung disease with the typical picture of bronchiectasis, chronic lung infection, and frequent pulmonary exacerbations with a decline in lung function (FEV_1) over time. The onset of symptomatic disease may be later and the slope of decline may be less steep compared with mutations with more detrimental effects on CFTR function. However, R117H-associated CF is still a progressive and life-shortening form of the disease. Similar to other patients with CF, patients with the R117H mutation are advised to perform chest physiotherapy and exercise and to take mucolytics (hypertonic saline and dornase alfa), anti-inflammatory agents (macrolides), bronchodilators and, if they are chronically infected with *Pseudomonas aeruginosa*, to use inhaled antibiotics. Pulmonary exacerbations are treated with oral or intravenous antibiotics. The treatment burden for patients with the R117H mutation is similar to the burden experienced by other patients with CF.

Patients with CF and the R117H mutation who will receive ivacaftor will all be followed in CF clinics by specialized physicians. The R117H mutation is identified in the standard genetic screening panel and 97% of CF patients have had genotyping done. Patients started on therapy will likely be those with evidence of lung disease based on pulmonary function, radiological imaging (i.e., evidence of bronchiectasis), and/or sputum culture. It is difficult to establish a threshold for initiating treatment based on FEV_1, as this measure is interpreted in the context of a patient's age and the nature of CF as a progressive disease. For example, a $ppFEV_1$ of 80% may be considered acceptable for a 55-year-old patient with CF but a similar value in a 20-year-old patient would be cause for concern. In addition, the expectation would be for patients with partial function mutations such as R117H to have better lung function than patients with more deleterious CFTR mutations. Adults with a $ppFEV_1$ greater than 90% and a lack of symptoms would likely be considered to have mild enough disease that treatment would not be initiated at that time. Patients who do not have significant lung disease (i.e., congenital bilateral absence of the vas deferens only) are unlikely to be treated.

Conclusions

In adult CF patients with the CFTR R117H mutation, ivacaftor was associated with modest, clinically relevant changes in $ppFEV_1$, relative to placebo. Ivacaftor also demonstrated clinically meaningful improvement in respiratory symptoms. No significant treatment effect was observed in the time to first pulmonary exacerbation or BMI over 24 weeks.

[1] Based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Ivacaftor treatment was associated with few serious adverse events or withdrawals due to adverse events in the KONDUCT trial or the 12-week interim analysis of the extension study. Considering the limited sample size and short duration of the studies, additional data are needed to determine the long-term safety of ivacaftor.

Given the relative rarity of the R117H mutation, the smaller size of the KONDUCT trial in relation to previous trials of ivacaftor is not surprising. However, this aspect of the trial likely limited study power, particularly for pulmonary exacerbations, as the adult subgroup that was the focus of this review comprised only 50 individuals. Due to the heterogeneous clinical course for those with the R117H mutation, caution may be warranted when generalizing the findings of the KONDUCT trial to Canadian CF patients with this mutation.

TABLE 1: SUMMARY OF KEY RESULTS IN KONDUCT TRIAL

Outcome	Overall Population (FAS)		Adults Subgroup (Aged ≥ 18 Years)	
	Placebo N = 35	Ivacaftor N = 34	Placebo N = 26	Ivacaftor N = 24
ppFEV$_1$				
Baseline, mean (SD)	70.2 (18.9)	75.7 (19.3)	62.2 (14.4)	67.0 (15.4)
Absolute change from baseline to week 24, LS mean (SE)	0.5 (1.1)	2.6 (1.2)	–0.5 (1.3)	4.5 (1.4)
Treatment difference ivacaftor versus placebo (95% CI), *P* value	2.1 (–1.1 to 5.4) *P* = 0.20		5.0 (1.1 to 8.8) *P* = 0.01	
Time to first pulmonary exacerbation				
Hazard ratio (95% CI), *P* value	0.93 (NR), *P* = 0.86		No significant differences (data not reported)	
CFQ-R respiratory domain score[a]				
Baseline, mean (SD)	66.4 (24.4)	75.3 (20.1)	59.9 (23.2)	68.4 (19.1)
Absolute change from baseline to week 24, LS mean (SE)	–0.8 (2.2)	7.6 (2.2)	–0.5 (2.6)	12.2 (2.7)
Treatment difference ivacaftor versus placebo (95% CI), *P* value	8.4 (2.2 to 14.6) *P* = 0.0091		12.6 (5.0 to 20.3) *P* = 0.002	
Drug discontinuation due to adverse event				
n (%)	0	0	0	0
Serious adverse events				
n (%)	6 (17)	4 (12)	6 (23)	2 (8)

CFQ-R = Cystic Fibrosis Questionnaire – Revised; CI = confidence interval; FAS = full analysis set; LS = least-squares; NR = not reported; ppFEV$_1$ = per cent predicted forced expiratory volume in 1 second; SD = standard deviation; SE = standard error.
[a] Higher CFQ-R scores represent better quality of life and positive treatment differences favour ivacaftor over placebo.
Source: Moss,[10] Clinical Study Report.[11]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Cystic fibrosis (CF), an autosomal recessive condition, is the most common fatal genetic disease affecting children and young adults in Canada.[1,2] It is caused by mutations in the CF transmembrane conductance Regulator (CFTR) gene, located on chromosome 7. The CFTR gene encodes a chloride channel that regulates ion and fluid transport across cell membranes.[1,2] When CFTR is dysfunctional, secretions become tenacious and sticky, resulting in pathology in multiple organs, including the lungs, large and small intestine, pancreatic and bile ducts, and vas deferens.[1]

More than 1,900 CFTR variants have been identified among CF patients.[1,2] 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).[1] 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 and the majority of these patients are pancreatic sufficient.[1]

The R117H-CFTR class IV gating mutation is a less common CFTR variant that is prevalent in approximately 3% of CF patients.[3,4] Based on data from the Canadian CF Patient Data Registry, the manufacturer has estimated there are 36 to 56 adult CF patients with the R117H mutation in Canada.[12] This may be an underestimate as some patients with the R117H mutation have CFTR-related disease but do not meet the diagnostic criteria for CF due to low sweat chloride levels (< 60 mmol/L). According to the clinical expert consulted for this review, these patients may be followed and treated in CF clinics but may not be captured in the CF Patient Registry.

The clinical course for patients with the R117H mutation is variable, ranging from asymptomatic to classic CF.[3,5] It is difficult to predict the pulmonary disease course, as other factors, such as environmental and modifier genes, also influence the CF phenotype.[1,5] In patients with the R117H mutation, the patient's phenotype is also influenced by the thymidine tract variant (at the end of intron 8).[1] A 5T thymidine tract will usually cause CF, whereas a 7T tract is more variably associated with CF.[1,5] The R117H 7T mutation is not in itself considered a disease-causing mutation; thus, patients with this mutation must have sweat chloride levels > 60 mmol/L to be diagnosed with CF. A 9T tract is typically not disease-causing.[1] In symptomatic patients with CF and the R117H mutation, pulmonary disease is progressive and associated with premature mortality.[6]

1.2 Standards of Therapy

The goals of CF therapy until now have been preservation of lung function by minimizing pulmonary infection and inflammation; restoration of baseline pulmonary function, symptoms, and level of inflammation after acute respiratory exacerbations; and maintenance of adequate nutrition. Respiratory treatments consist of physiotherapy and pharmacologic agents that include antibiotics, anti-inflammatory agents, and mucolytics. Nutritional treatments consist of high-calorie and high-fat diets and, for those with pancreatic insufficiency, pancreatic enzyme replacement. These treatments minimize the downstream effects of CF but do not address the underlying cause of the disease.

Patients state that managing CF requires a demanding treatment routine with regular visits to specialized CF clinics. The treatments, CF-related symptoms, infections, and hospitalizations take a toll on patients' emotional stamina and have a significant impact on day-to-day quality of life, affecting life decisions including education, career, travel, relationships, and family planning.

1.3 Drug

Ivacaftor has a Health Canada indication for the treatment of CF in patients aged 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, and in patients aged 18 years and older with an R117H mutation in the CFTR gene.[13] The Health Canada–recommended dose for adults is 150 mg every 12 hours, taken with fat-containing food.[13] 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. This results in improved functioning of multiple organs; most notably, the lungs and gastrointestinal tract.

Ivacaftor was previously reviewed by the CADTH Canadian Drug Expert Committee (CDEC) for the treatment of patients aged six years and older with CF and one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R. CDEC recommended that ivacaftor be listed on the condition of a substantial reduction in price.[14,15]

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2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of ivacaftor 150 mg tablet for the treatment of cystic fibrosis in patients aged 18 years or older with a R117H mutation of the CFTR gene.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Additional phase 3 studies were selected for inclusion based on the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients with cystic fibrosis who are aged 18 years or older and have a R117H mutation of the CFTR gene • Subgroups based on pulmonary disease severity
Intervention	Ivacaftor 150 mg every 12 hours, orally
Comparators	• Standard of care (may include antibiotics, anti-inflammatory agents, mucolytics, 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 **Other efficacy outcomes:** • Hospitalization • Weight or body mass index • Changes in concomitant CF medication • Sweat chloride levels **Harms outcomes:** • AEs, SAEs, WDAEs • Notable harms: hepatic AE
Study Design	Published and unpublished RCTs (excluding phase 1 and 2 studies if not considered a pivotal trial)

AE = adverse event; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; FEV_1 = forced expiratory volume in 1 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 via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Kalydeco (ivacaftor).

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 June 8, 2015. Regular alerts were established to update the search until the CDEC meeting in October 2015. 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, Databases (free), Internet Search and Open Access Journals. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (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

One study was 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 in Appendix 3: Excluded Studies.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

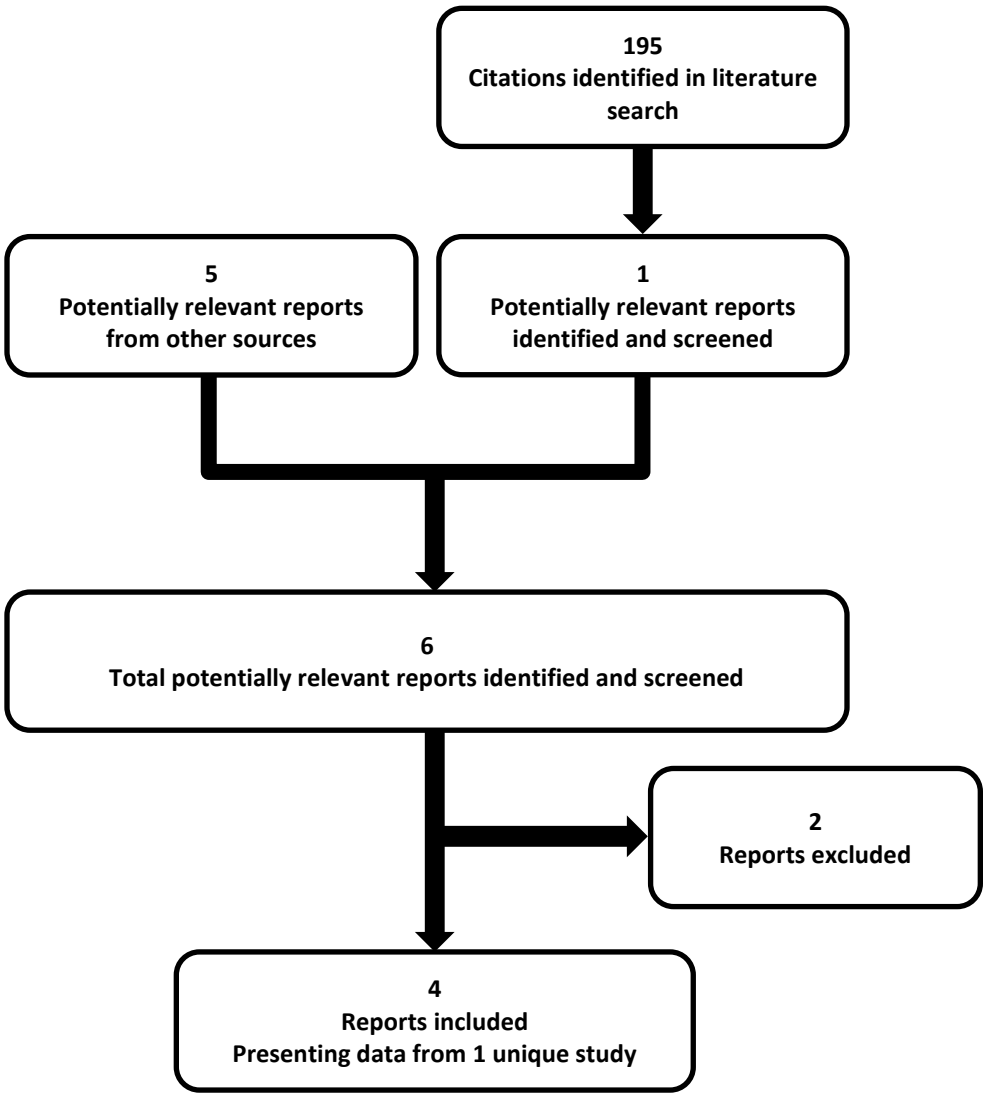


TABLE 3: DETAILS OF INCLUDED STUDIES

		KONDUCT (VX11-770-110)
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	North America and Europe
	Randomized (N)	70 (50 adults)
	Inclusion Criteria	• patients aged ≥ 6 years with confirmed diagnosis of CF[a] • chronic sinopulmonary disease • R117H mutation on at least one CFTR allele • $ppFEV_1$ ≥ 40 to ≤ 105 (age six to 11 years) or ≥ 40 to ≤ 90 (age ≥ 12 years)
	Exclusion Criteria	• CFTR gating mutation other than R117H[b] • chronic pulmonary infection with *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*
DRUGS	**Intervention**	Ivacaftor 150 mg every 12 hours, orally
	Comparator(s)	Placebo
DURATION	**Phase**	3
	Run-in	2 week
	Double-blind	24 weeks
	Follow-up	4 weeks
OUTCOMES	**Primary End Point**	Absolute change in $ppFEV_1$ from baseline to week 24
	Other End Points	Change from baseline in: • BMI • CFQ-R respiratory domain • sweat chloride Time to first pulmonary exacerbation Incidence in pulmonary exacerbations Harms
NOTES	**Publications**	Moss[10]

BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire – Revised; DB = double-blind; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; RCT = randomized controlled trial.

[a] Confirmation of CF diagnosis included sweat chloride value ≥ 60 mmol/L by quantitative pilocarpine iontophoresis or 2 CF-causing mutations.

[b] Any of the following mutations were excluded: G551D, G178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P, or G1349D.

Note: 2 additional reports were included (Health Canada Reviewer's Report,[16] Manufacturer's submission[12]).

Source: Moss,[10] Clinical Study Report.[11]

3.2 Included Studies

3.2.1 Description of Studies

One randomized, double-blind study met the inclusion criteria (KONDUCT). The safety and efficacy of 24 weeks of ivacaftor was compared with placebo in patients with confirmed CF and the R117H mutation on at least one CFTR allele. The primary outcome was the change from baseline in per cent predicted forced expiratory volume in 1 second ($ppFEV_1$) (Table 3). The trial was stopped early and, as a result, eight patients (total of four per group; [redacted]) did not complete the full 24 weeks of therapy. The reasons for early trial termination were not reported.

This review will focus on the results for the adult subgroup.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

In the KONDUCT trial, patients aged six years and older, with a confirmed diagnosis of CF, the R117H mutation, and chronic sinopulmonary disease, were enrolled (Table 3). For patients six to 11 years of age, the baseline $ppFEV_1$ had to be ≥ 40 to ≤ 105, and for those ≥ 12 years, $ppFEV_1$ ≥ 40 to ≤ 90 was required.

Those with severe pulmonary disease ($ppFEV_1$ < 40%) or with chronic pulmonary infection with *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus* were excluded. Also excluded were patients with an acute pulmonary exacerbation, organ transplant, or a CFTR mutation leading to a gating defect (G551D, G178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P, or G1349D).

b) Baseline Characteristics

In the KONDUCT trial, 70 patients were randomized but baseline characteristics were reported for the 69 patients who began treatment and who were analyzed. In the overall study population, 57% were female with a mean age ranging from 29.2 to 32.7 years. A total of 50 adults were enrolled, the majority (58%) of whom were women, with a mean age per group ranging from 37.5 to 40.6 years. The $ppFEV_1$ was lower in adults than in the overall population, and 54% to 58% of adults had a $ppFEV_1$ < 70%. A higher proportion of adults had the 5T variant of the R117H mutation.

The baseline characteristics showed some differences between treatment groups in the overall population and the subgroups. The ivacaftor group had higher $ppFEV_1$ and lower sweat chloride values than those in the placebo group, as well as fewer patients with the 5T CFTR variant, pancreatic insufficiency, and *Pseudomonas aeruginosa* infection at baseline. Of note, the number of patients per group was small (35 and 34 in the overall population; 26 and 24 in the adult subgroup; eight and nine in the child subgroup for placebo and ivacaftor, respectively).

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS IN KONDUCT TRIAL

	Overall Population		Adult Subgroup (≥ 18 Years)	
	Placebo N = 35	**Ivacaftor N = 34**	**Placebo N = 26**	**Ivacaftor N = 24**
Female, n (%)	20 (57)	19 (56)	16 (62)	13 (54)
Age, years, mean (SD)	32.7 (17.4)	29.2 (16·6)	40.6 (12.6)	37.5 (12.1)
≥ 18 years	26 (74)	24 (71)	--	--
12 to 17 years	1 (3)	1 (3)	--	--
6 to 11 years	8 (23)	9 (27)	--	--
Weight, kg, mean (SD)	62.8 (25.4)	66.1 (25.5)	71.7 (22.5)	77.9 (16.7)
BMI, mean (SD)	23.1 (6.0)	24.5 (6.3)	24.9 (5.7)	26.9 (5.2)
$ppFEV_1$, mean (SD)	70.2 (18.9)	75.7 (19.3)	62.2 (14.4)	67.0 (15.4)
< 70%, n (%)	15 (43)	13 (38)	15 (58)	13 (54)
≥ 70 to ≤ 90%, n (%)	14 (40)	14 (41)	11 (42)	10 (42)
> 90%, n (%)	6 (17)	7 (21)	0	1 (4)
Sweat chloride, mmol/L, mean (SD)	73.4 (19.7)	67.3 (23.5)	73.0 (17.3)	69.3 (24.1)
Respiratory domain of CFQ-R, mean (SD)	66.4 (24.4)	75.3 (20.1)	59.9 (23.2)	68.4 (19.1)
R117H poly-T status, n (%)				
5T	27 (77)	21 (62)	21 (81)	17 (71)
7T	7 (20)	12 (35)	4 (15)	6 (25)
Pancreatic insufficiency (fecal elastase-1 < 200 mcg/g), n (%)	5 (14)	2 (6)	5 (19)	2 (8)
Pseudomonas infection	19 (54)	15 (44)	[redacted]	[redacted]

BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire – Revised; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second; SD = standard deviation.
Source: Moss,[10] Clinical Study Report.[11]

3.2.3 Interventions

Patients were randomized in a 1:1 ratio, stratified by age group (six to 11, 12 to 17, and ≥ 18 years), and $ppFEV_1$ (< 70, ≥ 70 to ≤ 90, and > 90) to ivacaftor 150 mg every 12 hours or matched placebo for 24 weeks.

Use of inhaled hypertonic saline or inhaled antibiotics (cycling or continuous regimens) was allowed if patients were on a stable regimen before study entry. Patients not using inhaled hypertonic saline prior to the study were prohibited from initiating therapy during the study period. Patients starting antibiotics during the trial were classified as having an exacerbation. Use of cytochrome P450 CYP3A inhibitors or inducers, grapefruit, or Seville oranges were prohibited during the study. The use of key concomitant pulmonary medications is summarized in Table 5. [redacted]

TABLE 5: CONCOMITANT MEDICATIONS IN KONDUCT TRIAL

Drug	Placebo N = 35 n (%)	Ivacaftor N = 34 n (%)
Dornase alfa	[redacted]	[redacted]
Azithromycin	[redacted]	[redacted]
Tobramycin	[redacted]	[redacted]
Aztreonam lysine	[redacted]	[redacted]
Hypertonic saline	[redacted]	[redacted]

NR = not reported.
Source: Clinical Study Report.[11]

3.2.4 Outcomes

The primary outcome in the KONDUCT trial was the absolute change from baseline in the $ppFEV_1$ over 24 weeks. Secondary outcomes included body mass index (BMI) (kg/m^2), sweat chloride, respiratory domain of the Cystic Fibrosis Questionnaire – Revised (CFQ-R), and time to first pulmonary exacerbation.

$ppFEV_1$ measures the maximum volume of air forcefully exhaled in one second, expressed as a percentage of the normal predicted value adjusted for age, sex, and body composition. FEV_1 is an accepted end point for assessing pulmonary function in obstructive diseases and has been shown to relate to morbidity, disease progression, and mortality in CF. However, there are no published data on the clinically meaningful magnitude of change in FEV_1 in CF (Appendix 5: Validity of Outcomes). In the KONDUCT trial, spirometry was performed according to the American Thoracic Society Guidelines.

The sweat chloride test is a standard diagnostic tool for CF and is a biomarker of CFTR ion channel activity. It is not known, however, whether reductions in sweat chloride as a result of treatment relate to clinically beneficial effects.[17]

The CFQ-R is a disease-specific quality of life instrument designed for patients with CF. It consists of three modules that measure quality of life, symptoms (including a respiratory domain), and health perceptions over a two-week recall period. The respiratory symptom scale was included as a secondary outcome in KONDUCT. This scale consists of six questions regarding the presence of congestion, daytime cough, presence of mucus upon coughing, wheezing, trouble breathing, and waking during the night because of coughing, answered on a four-category ordinal scale: “a great deal,” “somewhat,” “little,” “not at all.”[18-20] The respiratory domain of the CFQ-R scale is scored from 0 to 100 points, with higher scores indicating fewer respiratory symptoms, and the minimal clinically important difference (MCID) is considered to be 4.0 points for patients with stable disease and 8.5 points for patients with an exacerbation.[21]

In the KONDUCT trial, a pulmonary exacerbation was defined as new, or change in, antibiotic therapy (intravenous, inhaled, or oral) for any four or more of the following signs or symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10%; and radiographic changes indicative of pulmonary infection.

An adverse event was defined as any untoward medical occurrence in a patient during the study that may or may not have had a causal relationship with the treatment. This included any newly occurring

event or previous condition that had increased in severity or frequency after entering the study, up until the follow-up visit, four weeks after the end of treatment.

A serious adverse event was defined as any untoward medical occurrence that resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, led to a congenital anomaly or birth defect, or was another important medical event that may have required intervention or exposed the patient to danger.

3.2.5 Statistical Analysis

Study enrolment was planned for a minimum of 40 and a maximum of 80 patients, with estimated study power calculated based on results from previous ivacaftor trials and a review of the CF literature. A sample size of 60 patients would provide 80% power to detect a 6% difference in absolute change from baseline in $ppFEV_1$, at a 5% level of significance.

The primary outcome was analyzed using a mixed effects model for repeated measurements (MMRM), which included the absolute change from baseline in $ppFEV_1$ as the dependent variable, treatment (ivacaftor versus placebo), visit (week 2, 4, 8, 16, and 24), and treatment by visit interaction as fixed effects, and subject as a random effect, with adjustment for the continuous baseline values of age and $ppFEV_1$. Data were assumed missing at random and no imputation of missing data. For the primary outcome, the extent of missing data at different time points ranged from none missing at week 2, to four placebo patients (11%) and six ivacaftor patients (18%) with missing data at week 24.

Sensitivity analyses were conducted for the primary outcome to assess the impact of missing data. Missing post-baseline values were imputed using different imputation methods, including a "dropout" reason-based imputation approach and pattern mixture model. Additional sensitivity analyses using a non-parametric test (stratified Wilcoxon rank-sum test) and the per-protocol and complete case sets were also conducted.

The continuous secondary outcomes of sweat chloride and CFQ-R respiratory domain were analyzed with an MMRM model similar to the primary outcome, with the addition of the baseline sweat chloride or CFQ-R respiratory domain score as a covariate. The rate of change of BMI from baseline over 24 weeks was obtained from a linear mixed effects model with BMI as the dependent variable and treatment as a fixed effect. Adjustment for baseline $ppFEV_1$, age and visit by treatment interaction were included as covariates. Time to first pulmonary exacerbation was analyzed using a Cox regression model adjusted for age group and $ppFEV_1$ severity at baseline. Counts of pulmonary exacerbations (a tertiary outcome) were analyzed using negative binomial regression adjusting for age and baseline $ppFEV_1$.

Pre-specified subgroup analyses were conducted based on age group, baseline $ppFEV_1$, sex, geographic region, *Pseudomonas* infection at baseline, and R117H poly-T variant (5T, 7T, 9T). Of note, randomization was stratified by age (six to 11, 12 to 17, and ≥ 18 years), and $ppFEV_1$ (< 70, ≥ 70 to ≤ 90, and > 90).

There was no information provided on methods to control for type I error across the multiple efficacy outcomes and subgroup analyses conducted. There was no imputation of missing data for secondary or safety outcomes.

a) Analysis Populations

The analysis of efficacy and safety outcomes was based on a modified intention-to-treat population that included all randomized patients who received at least one dose of study drug (full analysis set [FAS]). The per-protocol set (PPS) included all patients in the FAS without any major protocol violations. Due to the premature termination of the study, a complete case set (CCS) was also analyzed, which included all patients in the FAS who completed the full 24-week treatment period.

3.2.6 Patient Disposition

A total of 70 patients were randomized and three patients (4%) discontinued treatment early (pregnancy, non-compliance, or did not initiate therapy) (Table 6). An additional eight patients (four per group) had treatment stopped prior to completing 24 weeks, when the manufacturer terminated the clinical trial.

TABLE 6: PATIENT DISPOSITION

	KONDUCT	
	Placebo	Ivacaftor
Screened, N	108	
Randomized, N (%)	70 (65)	
	36	34
Discontinued, N (%)	1 (3)	2 (6)
Not treated	1 (3)	0
Non-compliance	0	1 (3)
Pregnancy	0	1 (3)
FAS, N	35	34
PPS, N	33	30
CCS,[a] N	31	30
Safety, N	35	34

CCS = complete case set; FAS = full analysis set; PPS = per-protocol set.
[a] The CCS included all randomized patients who had the opportunity to complete 24 weeks of therapy. The study was stopped early and thus 4 patients in each group were unable to complete the full 24-week treatment period.
Source: Clinical Study Report.[11]

3.3 Exposure to Study Treatments

The mean exposure was 22.3 weeks for placebo and 21.6 weeks for ivacaftor groups in the KONDUCT trial.

3.4 Critical Appraisal

3.4.1 Internal Validity

Patients were randomized using appropriate methods and adequate allocation concealment. The randomization sequence was generated by the sponsor and patients were allocated to treatments using an interactive Web response system. Matched placebo was used to maintain blinding. There were some differences in the frequency of adverse events between groups. However, it is unlikely that a substantial proportion of patients could have ascertained treatment assignment due to these differences.

There were some differences in the baseline characteristics suggesting that patients in the ivacaftor group had less severe CF disease compared with the placebo group. The ivacaftor group had higher ppFEV$_1$ and lower sweat chloride values than those in the placebo group, as well as fewer patients with the 5T CFTR variant, pancreatic insufficiency and Pseudomonas infection at baseline. These differences

may have arisen by chance as a result of the small number of patients randomized per group. While the health status and prognosis of patients in the ivacaftor group may have been somewhat better compared with the placebo group, analyses for the main efficacy outcomes were adjusted for baseline values, which should have corrected for any imbalances. Conceivably, the observed imbalances could impart bias in the analysis if the degree of improvement with ivacaftor is dependent on any of the baseline variables that were found to differ between groups. For example, should patients with baseline ppFEV$_1$ near normal values encounter ceiling effects, and if more such patients are randomized to active treatment compared with placebo, the observed efficacy of treatment may be diminished. However, the imbalances in baseline characteristics do not appear to be sufficiently extreme to warrant significant concern.

Overall, few patients withdrew from treatment prematurely (4%), and four patients per group were unable to complete the entire treatment duration due to the early termination of the trial. The manufacturer did not report the rationale for the early termination of the trial. In response to CADTH's request for further information regarding the reason for early termination, the manufacturer responded that the total enrolment was at the high end of the planned range and eight of a total of 70 patients were receiving blinded treatment at time of study closure. Furthermore, all enrolled patients pursued treatment in rollover study 112 and sensitivity analysis with and without data from these eight patients did not alter study conclusions.

Analysis of the FAS represented a modified intention-to-treat analysis as the FAS included those patients who were randomized and who received at least one dose of a study drug.

The proportion of patients with missing ppFEV$_1$ data at various time points ranged from [redacted] at week 2 to [redacted] (placebo) and [redacted] (ivacaftor) at week 24. The use of an MMRM model assumed missing at random (MAR). This assumption may not hold because missed visits can result from non-random events such as poorly controlled symptoms or exacerbations. However, the concern that this may introduce bias in the results is mitigated by the fact that the primary outcome analysis, with no imputation for missing data, showed comparable results to sensitivity analyses that imputed missing data using two different methods. Another potential issue with the statistical analysis is whether the sample size was sufficient for multivariable regression modelling analysis that included three covariates (age, baseline value, visit, and treatment by visit interaction).

The manufacturer analyzed multiple key secondary outcomes and subgroups, but did not institute procedures to control for multiplicity of statistical testing. Thus, the interpretation of statistically significant results, such as for CFQ-R, should be made with caution due to the inflated type I error.

The adult subgroup data were used to support the regulatory approval of ivacaftor, even though the study failed its primary outcome.[16] While the subgroup analyses were pre-specified and randomization was stratified by age group, the subgroup analyses were limited by the small number of patients and were likely underpowered. The power calculations indicated that the study had only about 60% power to detect a 5% absolute difference in FEV$_1$ if 50 patients (the size of the adult subgroup) were randomized. However, the small sample size of the KONDUCT trial compared with previous trials of ivacaftor is perhaps not surprising given the low prevalence of the R117H mutation.

3.4.2 External Validity

The R117H-7T mutation is not considered a disease-causing mutation; patients with this mutation require sweat chloride levels of > 60 mmol/L to be diagnosed as having CF. The KONDUCT trial permitted

the inclusion of patients with R117H-7T. However, based on the baseline demographic data presented in Table 4, it appears unlikely that all patients with the R117H-7T mutation had sweat chloride levels above 60 mmol/L. The ivacaftor arm had a mean sweat chloride level of 67.3 mmol/L and 35% of patients had the 7T variant. Furthermore, the mean baseline sweat chloride levels among the 10 adults with the 7T variant were less than 60 mmol/L (56 mmol/L and 39 mmol/L in the placebo and ivacaftor arms, respectively). Therefore, it is clear that some adults with the 7T variant enrolled in KONDUCT would not meet the criteria for the diagnosis of CF. Inclusion of these patients with milder disease in the trial may have attenuated the apparent efficacy of ivacaftor versus placebo. Apart from this concern, the clinical expert consulted for this review considered that patients enrolled in KONDUCT were largely representative of patients with the R117H mutation and pulmonary disease observed in clinical practice. However, there are patients with the R117H mutation without pulmonary disease who are followed by CF specialists for other manifestations (e.g., infertility); such patients are not reflected in the KONDUCT sample, nor are they candidates for treatment with ivacaftor.

Unlike CF patients with G551D mutation, the clinical course for individuals with the R117H mutation is highly variable; it is therefore difficult to identify which patients will develop progressive pulmonary disease and benefit most from treatment. The treatment effects observed in the KONDUCT trial may be generalizable only to adult CF patients with characteristics similar to those enrolled; that is, patients with moderately severe pulmonary disease. It is unclear if ivacaftor would benefit adult patients with preserved pulmonary function as no data were available for those with a $ppFEV_1 > 90\%$. Moreover, patients with severe pulmonary disease at baseline ($ppFEV_1 < 40\%$) were excluded).

The KONDUCT study measured clinically relevant outcomes including pulmonary function ($ppFEV_1$), respiratory symptoms, BMI, and pulmonary exacerbations. However, it was able to demonstrate a treatment benefit only for $ppFEV_1$ and respiratory symptoms.

3.5 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in Section 2.2, Table 2. See APPENDIX 4: for detailed efficacy data.

No data were available for the following outcomes: health-related quality of life, hospitalizations, or change in concomitant CF medications. Deaths were reported only as a safety outcome.

3.5.1 Pulmonary Function (FEV_1)

In the overall KONDUCT study population, the mean $ppFEV_1$ values at baseline were 70.2% and 75.7% in the placebo and ivacaftor groups, respectively. Both groups showed an increase in the mean $ppFEV_1$ values from baseline to week 24 (placebo 0.5% versus ivacaftor 2.6%). However, the treatment difference did not reach statistical significance (mean difference 2.1%; 95% CI, –1.1% to 5.4%) (Table 7 and Appendix 4, Figure 2). The results of the sensitivity analyses were consistent with the primary analysis.

In the adult subgroup (N = 50), the baseline $ppFEV_1$ values were lower (placebo: 62.2%, ivacaftor: 67%) than in the younger subgroup (children aged six to 11 years; $ppFEV_1$, 94.0% and 97.5%) (Table 7). In adults, the mean absolute change from baseline in $ppFEV_1$ was –0.5% in the placebo group and 4.5% in the ivacaftor group. The mean difference in $ppFEV_1$ was statistically significant, favouring ivacaftor (5.0%; 95% CI, 1.1% to 8.8%, $P = 0.01$) (Appendix 4, Figure 3). Although there is no MCID reported in the literature for this outcome, the clinical expert consulted for this review indicated that this treatment difference is clinically meaningful.

TABLE 7: SUMMARY OF EFFICACY OUTCOMES FOR KONDUCT TRIAL

Outcome	Overall Population (FAS)		Adult Subgroup (Aged ≥ 18 Years)	
ppFEV$_1$	**Placebo N = 35**	**Ivacaftor N = 34**	**Placebo N = 26**	**Ivacaftor N = 24**
Baseline, mean (SD)	70.2 (18.9)	75.7 (19.3)	62.2 (14.4)	67.0 (15.4)
Absolute change from baseline to week 24, LS mean (SE)	0.5 (1.1)	2.6 (1.2)	–0.5 (1.3)	4.5 (1.4)
Treatment difference ivacaftor versus placebo (95% CI), *P* value	2.1 (–1.1 to 5.4) *P* = 0.20		5.0 (1.1 to 8.8) *P* = 0.01	
Time to first pulmonary exacerbation	**N = 35**	**N = 34**		
Hazard ratio (95% CI), *P* value	0.93 (NR), *P* = 0.86		No significant differences (data not reported)	
Incidence of pulmonary exacerbations	**N = 35**	**N = 34**		
Number of patients with event	13	11	NR	
Number of events	17	13	NR	
Event rate	0.295	0.249	NR	
Rate ratio (95% CI)	[redacted]		NR	
CFQ-R respiratory domain score[a]	**N = 34**	**N = 33**	**N = 26**	**N = 24**
Baseline, mean (SD)	66.4 (24.4)	75.3 (20.1)	59.9 (23.2)	68.4 (19.1)
Absolute change from baseline to week 24, LS mean (SE)	–0.8 (2.2)	7.6 (2.2)	–0.5 (2.6)	12.2 (2.7)
Treatment difference ivacaftor versus placebo (95% CI), *P* value	8.4 (2.2 to 14.6) *P* = 0.0091		12.6 (5.0 to 20.3) *P* = 0.002	
BMI (kg/m^2)	**N = 35**	**N = 34**	**N = 26**	**N = 24**
Baseline, mean (SD)	23.1 (6.0)	24.5 (6.3)	24.9 (5.7)	26.9 (5.2)
Mean rate of change from baseline to week 24, LS mean (SE)	0.2 (0.7)	0.5 (0.7)	0.2 (0.8)	0.5 (0.8)
Treatment difference ivacaftor versus placebo (95% CI), *P* value	0.3 (–1.6 to 2.1) *P* = 0.78		0.3 (–1.9 to 2.5) *P* = 0.78	
Sweat chloride (mmol/L)	**N = 35**	**N = 32**	**N = 26**	**N = 23**
Baseline, mean (SD)	73.4 (19.7)	67.3 (23.5)	73.0 (17.3)	69.3 (24.1)
Absolute change from baseline to week 24, LS mean (SE)	–2.3 (1.4)	–26.3 (1.5)	–4.0 (1.5)	–25.9 (1.6)
Treatment difference ivacaftor versus placebo (95% CI), *P* value	–24.0 (–28.0 to –19.9) *P* < 0.0001		-21.9 (–26.5 to –17.3) *P* < 0.0001	

BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire – Revised; CI = confidence interval; FAS = full analysis set; LS = least-squares; NR = not reported; ppFEV$_1$ = per cent predicted forced expiratory volume in 1 second; SD = standard deviation; SE = standard error.

[a] Higher CFQ-R scores represent better quality of life and positive treatment differences favour ivacaftor over placebo.

Source: Moss,[10] Clinical Study Report.[11]

A responder analysis was conducted as a tertiary outcome (Appendix 4, Table 10). More patients in the ivacaftor group than in placebo had an absolute increase ≥ 5% in ppFEV$_1$ from baseline to week 24 in the FAS (38% versus 20%) and adult subgroup [redacted]. The

same trend was noted for the proportion with a 10% or greater increase in $ppFEV_1$ (ivacaftor versus placebo FAS: 15% versus 6%, [redacted].

Additional subgroup analyses according to baseline $ppFEV_1$ were also reported (Appendix 4, Table 9). For the overall trial population, no statistically significant differences were found in the change from baseline in $ppFEV_1$ within subgroups with baseline $ppFEV_1$ < 70%, between 70% and 90%, and > 90% (no *P* value reported for interaction between treatment and baseline $ppFEV_1$ category). Post hoc subgroup analyses by baseline pulmonary function in adults showed statistically significant differences favouring ivacaftor in adults with baseline $ppFEV_1$ between 70% and 90%, but not in adults with $ppFEV_1$ < 70%. No adults had a baseline $ppFEV_1$ > 90%. The subgroup analyses based on baseline $ppFEV_1$ should be interpreted with caution considering the small numbers of patients in the subgroups.

3.5.2 Acute Pulmonary Exacerbations

During the 24-week study period, 13 patients in the placebo group experienced 17 pulmonary exacerbations, and 11 patients had 13 events in the ivacaftor group among the overall KONDUCT population. The event rate for pulmonary exacerbations was 0.249 for the ivacaftor and 0.295 for the placebo group) and the rate ratio [redacted]. The time to first pulmonary exacerbation was also not statistically significantly different between groups (hazard ratio 0.93, *P* = 0.86) (Table 7). No clinically relevant differences were detected between groups in the time to first pulmonary exacerbation among the adult subgroup (Appendix 4, Figure 4).

3.5.3 Respiratory Symptoms

In the KONDUCT trial at baseline, the CFQ-R respiratory domain scores were higher in the ivacaftor group than placebo in the overall population (75.3 versus 66.4 points) and adult subgroup (68.4 versus 59.9 points), indicating fewer respiratory symptoms for ivacaftor patients (Table 7). Over 24 weeks, mean scores decreased for placebo and increased for ivacaftor. The treatment differences were statistically significant favouring ivacaftor, and exceeded the MCID of 4.0 points, in both the overall population (8.4 points) and the adult subgroup (12.6 points).

3.5.4 Body Mass Index

The mean BMI at baseline was 23.1 kg/m^2 for placebo and 24.5 kg/m^2 for the ivacaftor group in the overall KONDUCT study population, and 24.9 kg/m^2 and 26.9 kg/m^2 in the adult subgroup (Table 7). Over 24 weeks, the mean BMI increased 0.2 kg/m^2 to 0.5 kg/m^2, in the overall population and adult subgroup, with no clinically or statistically significant changes noted between treatments.

3.5.5 Sweat Chloride Levels

In the overall KONDUCT study population, the baseline sweat chloride levels were 73.4 mmol/L and 67.3 mmol/L in the placebo and ivacaftor groups, respectively (Table 7). Over 24 weeks, the mean values decreased by 2.3 mmol/L and 26.3 mmol/L in the placebo and ivacaftor groups, respectively, and the treatment difference was statistically significantly different favouring ivacaftor (mean difference –24.0 mmol/L; 95% CI, –28.0 to –19.9, *P* < 0.0001). The findings were similar in the adult subgroup, with statistically significant differences favouring ivacaftor (mean difference –21.9 mmol/L; 95% CI, –26.5 to –17.3, *P* < 0.0001).

3.6 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See APPENDIX 4: for detailed harms data.

3.6.1 Adverse Events

In the KONDUCT trial, most patients reported an adverse event during the study period (placebo 100%, ivacaftor 94%) (Table 8). Infective pulmonary exacerbations and cough were the most frequently reported events in both treatment groups for the overall study population. Numerically more patients who received ivacaftor reported oropharyngeal pain (15% versus 6 %), nasal congestion (15% versus 6%), wheezing (12% versus 3%) or abdominal pain (12% versus 0%) compared with placebo, whereas fewer patients on ivacaftor than placebo reported hemoptysis (0% versus 6%), pyrexia (6% versus 17%), or arthralgia (0% versus 11%); however, these percentages should be interpreted with caution, considering the small number of patients enrolled.

The adverse events reported in the adult subgroup were similar to those reported in the overall population (Table 8).

3.6.2 Serious Adverse Events

Six patients on placebo (17%) and four patients on ivacaftor (12%) reported a serious adverse event (Table 8). Infective pulmonary exacerbation of CF was the most frequent serious adverse event in both groups. Cellulitis and constipation were reported as serious adverse events, each in one patient treated with ivacaftor.

TABLE 8: HARMS IN KONDUCT TRIAL

	Overall Population (FAS)		Adult Subgroup (Aged ≥ 18 Years)	
Adverse Events	**Placebo N = 35**	**Ivacaftor N = 34**	**Placebo N = 26**	**Ivacaftor N = 24**
Patients with ≥ 1 adverse events, n (%)	35 (100)	32 (94)	26 (100)	23 (96)
Common adverse events, n (%) (incidence ≥ 10% of patients per either group)				
Infective pulmonary exacerbation of CF	14 (40)	13 (38)	13 (50)	11 (46)
Upper respiratory tract infection	5 (14)	3 (9)	5 (19)	2 (8)
Sinusitis	5 (14)	2 (6)	3 (12)	1 (4)
Cough	9 (26)	10 (29)	7 (27)	9 (38)
Sputum increased	4 (12)	5 (15)	4 (15)	5 (21)
Nasal congestion	2 (6)	5 (15)	1 (4)	5 (21)
Oropharyngeal pain	2 (6)	5 (15)	0	4 (17)
Wheezing	1 (3)	4 (12)	1 (4)	4 (17)
Hemoptysis	6 (17)	0	6 (23)	0
Headache	5 (14)	6 (18)	3 (12)	4 (17)
Diarrhea	4 (12)	5 (15)	3 (12)	4 (17)
Abdominal pain	0	4 (12)	0	2 (8)
Vomiting	4 (11)	3 (9)	3 (12)	2 (8)
Pyrexia	6 (17)	2 (6)	3 (12)	1 (4)
Arthralgia	4 (11)	0	3 (12)	0
Serious adverse events, n (%)	6 (17)	4 (12)	6 (23)	2 (8)
Infective pulmonary exacerbation of CF	6 (17)	3 (9)	6 (23)	2 (8)

	Overall Population (FAS)		Adult Subgroup (Aged ≥ 18 Years)	
Adverse Events	**Placebo N = 35**	**Ivacaftor N = 34**	**Placebo N = 26**	**Ivacaftor N = 24**
Cellulitis	0	1 (3)	0	1 (4)
Constipation	0	1 (3)	0	0
Drug discontinuation due to adverse event, n (%)	0	0	0	0
Deaths, n (%)	0	0	0	0

CF = cystic fibrosis; FAS= full analysis set.
Source: Clinical Study Report.[11]

3.6.3 Withdrawals Due to Adverse Events

No patients in either group stopped therapy due to adverse events.

3.6.4 Mortality

No deaths were reported during the KONDUCT trial.

3.6.5 Notable Harms

In the protocol, liver-related adverse events were identified as a notable adverse event for ivacaftor. Data on the proportion of patients with alanine transaminase (ALT), aspartate transaminase (AST), or total bilirubin levels > 2 times the upper limit of normal are reported in Appendix 4, Table 10. Two patients on placebo and three patients on ivacaftor had elevated ALT levels and one patient on ivacaftor had elevated AST levels during treatment. No patients had bilirubin levels that exceeded two times the upper limit of normal. No clear pattern of elevated liver function tests and no other liver-related adverse events were noted for the study drug.

4. DISCUSSION

4.1 Summary of Available Evidence

One randomized, double-blind study (KONDUCT) met the inclusion criteria for this review. The safety and efficacy of 24 weeks of ivacaftor (150 mg every 12 hours) was compared with placebo in patients aged six years or older with confirmed CF and the R117H mutation on at least one CFTR allele. The primary outcome was the change from baseline in $ppFEV_1$ and secondary outcomes included pulmonary exacerbations, respiratory symptoms, BMI, and sweat chloride levels.

Key limitations were the small sample size, and inflated type I error for secondary outcomes due to multiple statistical testing without application of a correction procedure.

4.2 Interpretation of Results

4.2.1 Efficacy

From the patient group input received by CDR on this submission, it is clear that patients consider improved lung function to be an important outcome of treatment. In the KONDUCT trial, ivacaftor was not associated with a statistically significant increase in $ppFEV_1$, relative to placebo for the overall trial population of patients with CF and the R117H mutation. Similarly, no statistically significant differences were found in the time to first pulmonary exacerbation or change in BMI. However, ivacaftor was associated with statistically and clinically significant improvement in respiratory symptoms as measured by CFQ-R. Sweat chloride levels were also statistically significantly reduced, although the clinical relevance of treatment-related changes in sweat chloride levels is not known. In the pre-specified subgroup analyses by age, adults treated with ivacaftor showed a statistically significant 5% increase in $ppFEV_1$ versus placebo. Among adults, 13 (54%) individuals in the ivacaftor group achieved a ≥ 5% absolute increase in $ppFEV_1$ compared with four (15%) in the placebo group. Adults who received ivacaftor also reported a clinically important improvement in respiratory symptoms, based on CFQ-R respiratory symptom domain scores, but there was no significant difference in the rate of acute exacerbations. In the open-label extension study, the adult subgroup (n = 46) reported increased $ppFEV_1$ (5.2%) and CFQ-R respiratory domain scores (12.3 points) after an additional 12 weeks of ivacaftor therapy.

The observed treatment effects in KONDUCT were smaller in magnitude than those observed in ivacaftor clinical trials that enrolled patients with a G551D or non-G551D gating mutation. The absolute change in $ppFEV_1$ for ivacaftor versus placebo ranged from 10.6% to 12.5% in the STRIVE, ENVISION, and KONNECTION trials.[7-9] In these trials, ivacaftor was also associated with statistically significant reductions in pulmonary exacerbations[8] and increases in BMI (0.7 kg/m^2)[9] or body weight (1.9 kg to 2.8 kg),[7,8] and increased (i.e., improved) CFQ-R respiratory domain scores (ranging from 6.1 to 9.6 points),[7-9] relative to placebo. However, the patients in these trials had more severe CF and the majority had pancreatic insufficiency. Considering that the CF clinical course for individuals with the R117H mutation is highly heterogeneous, and generally of a milder severity, it is perhaps not surprising that the observed effect sizes on $ppFEV_1$ were smaller than in trials of patients with other mutations. As well, the KONDUCT trial may have been underpowered to detect differences between treatments, or of insufficient duration for outcomes such as pulmonary exacerbations. As such, the impact of ivacaftor on pulmonary exacerbations in patients with R117H mutation is unclear, based on the data available currently. The lack of significant increases in BMI is also not unexpected, given that baseline BMI values were in the normal range and only seven of 69 patients (10%) were pancreatic-insufficient in the KONDUCT trial. The 5% increase in $ppFEV_1$ observed in the adult subgroup was interpreted as clinically meaningful by the clinical expert consulted for this review. The limited sample size and duration (24 weeks) of the

KONDUCT trial was insufficient to examine differences in survival with ivacaftor. However, maintenance of pulmonary function (i.e., higher ppFEV$_1$) has been associated with reduced morbidity and mortality in CF.

Ivacaftor is a first-in-class drug; thus, comparison with placebo was considered to be appropriate. However, it is important to note that ivacaftor was studied as an add-on to a stable regimen of CF medications. There is no 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 and burden associated with administering other treatments. Treatment burden was a major concern expressed by patients with CF in the input received by CDR.

4.2.2 Harms

No deaths were reported in the 24-week KONDUCT trial and no patients discontinued therapy due to adverse events. Ten patients reported serious adverse events during the KONDUCT trial (placebo: six; ivacaftor: four) and eight patients reported a serious adverse event in the first 12 weeks of the open-label extension study (Appendix 6: Summary of Open-Label Extension Study). Pulmonary exacerbation was the most frequently reported serious adverse event in both studies.

In the KONDUCT study, the most common adverse events were pulmonary exacerbations and cough. Similar to the other gating mutation trials,[7-9] numerically more patients in the ivacaftor group reported oropharyngeal pain, nasal congestion, or abdominal pain, than placebo. No clear pattern of elevated liver function tests and no other liver-related adverse events were noted in the KONDUCT study. It should be noted that the incidence of adverse effects is difficult to estimate from the KONDUCT trial due to the small sample size, but the available data do not raise any new concerns compared with previous trials of ivacaftor for patients with other CFTR mutations. Additional data are needed to determine the long-term safety of ivacaftor.

4.2.3 Potential Place in Therapy[2]

In contrast with patients with CF who carry two copies of CF mutations that confer no or minimal CFTR function (e.g., F508del, G551D, G542X), people with CF who have the R117H mutation have a more heterogeneous clinical phenotype with a broader range of lung function for a given age and with more variability in disease manifestations (e.g., pancreatic sufficiency, acute pancreatitis). While it can be difficult to predict the prognosis and clinical phenotype for an individual with CF and the R117H mutation, the majority will have progressive lung disease with the typical picture of bronchiectasis, chronic lung infection, and frequent pulmonary exacerbations with a decline in lung function (FEV$_1$) over time. The onset of symptomatic disease may be later and the slope of decline may be less steep compared with mutations with more detrimental effects on CFTR function. However, R117H-associated CF is still a progressive and life-shortening form of the disease.

Chronic pulmonary therapy is determined by impairment of lung function and presence of bacterial pathogens. Similar to other patients with CF, patients with the R117H mutation are advised to perform chest physiotherapy and exercise and to take mucolytics (hypertonic saline and dornase alfa), anti-inflammatory agents (macrolides), bronchodilators and, if they are chronically infected with *Pseudomonas* , to use inhaled antibiotics.[22] These patients are less likely to require pancreatic enzymes but will need vitamin supplementation. Pulmonary exacerbations are treated with oral or intravenous antibiotics. These treatments slow, but do not halt, the decline in lung function. The treatment burden for patients with the R117H mutation is similar to the burden experienced by other patients with CF.

[2] Based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Ivacaftor for R117H has been shown in the KONDUCT trial to have modest but clinically significant improvements in FEV_1 in the subgroup of adults with CF and the R117H mutation. It is notable that the degree of improvement in FEV_1 seen with ivacaftor is slightly larger than the improvement in FEV_1 seen in a phase 3 trial of dornase alfa (Pulmozyme) (a relative increase of 5.8% in FEV_1 over six months).[23] Observational data suggest that use of dornase alfa may be associated with a significant reduction in lung function decline[24] and improvement in survival.[25] Thus, the magnitude of change observed in KONDUCT with ivacaftor may be significant. No effect on exacerbation rates was seen, although the limited sample size of the trial and relatively low event rates may have limited study power for this outcome.

Patients with CF and the R117H mutation who will receive ivacaftor will all be followed in CF clinics by specialized physicians. The R117H mutation is identified in the standard genetic screening panel and 97% of CF patients have had genotyping done.[26] Patients started on therapy will likely be those with evidence of lung disease based on pulmonary function, radiological imaging (i.e., evidence of bronchiectasis), and/or sputum culture. It is difficult to establish a threshold for initiating treatment based on FEV_1, as this measure is interpreted in the context of a patient's age and the nature of CF as a progressive disease. For example, a $ppFEV_1$ of 80% may be considered acceptable for a 55-year-old patient with CF, but a similar value in a 20-year-old patient would be cause for concern. In addition, the expectation would be for patients with partial function mutations such as R117H to have better lung function than patients with more deleterious CFTR mutations. Adults with a $ppFEV_1 > 90\%$ and a lack of symptoms would likely be considered to have a mild enough disease that treatment would not be initiated at that time.

Patients who do not have significant lung disease (i.e., congenital bilateral absence of the vas deferens only) are unlikely to be treated. Patients enrolled in CF centres submit data annually to CF Canada's Patient Data Registry, which tracks lung function, hospital admissions, and CF drug use. Thus, there is the possibility of tracking the real-world impact of ivacaftor in this population over time.

5. CONCLUSIONS

In adult CF patients with the CFTR R117H mutation, ivacaftor was associated with modest, clinically relevant changes in ppFEV$_1$, relative to placebo. Ivacaftor also demonstrated clinically meaningful improvement in respiratory symptoms. No significant treatment effect was observed in the time to first pulmonary exacerbation over 24 weeks.

Ivacaftor treatment was associated with few serious adverse events or withdrawals due to adverse events in the KONDUCT trial or the 12-week interim analysis of the extension study. Considering the limited sample size and short duration of the studies, additional data are needed to determine the long-term safety of ivacaftor.

Given the relative rarity of the R117H mutation, the smaller size of the KONDUCT trial in relation to previous trials of ivacaftor is not surprising. However, this aspect of the trial likely limited study power, particularly for pulmonary exacerbations, as the adult subgroup that was the focus of this review comprised only 50 individuals. Due to the heterogeneous clinical course for those with the R117H mutation, caution may be warranted when generalizing the findings of the KONDUCT trial to Canadian CF patients with this mutation.

APPENDIX 1: PATIENT INPUT SUMMARY

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

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

One patient group, Cystic Fibrosis Canada (CF Canada), 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. CF Canada has received financial contributions from pharmaceutical companies, including Vertex. Contributions from pharmaceutical companies accounted for less than 2% of the organization's gross revenue in 2014–2015. CF Canada made no statement with regard to conflicts of interest for the individuals who prepared their submission.

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 55 patients aged 18 years and older have the R117H mutation. The disease causes the body to produce thick, sticky mucus 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 40 CF patients who died in 2013, half were younger than 35 years of age.

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

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

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. Inhaled medications are used daily to open the airways. The total time spent

on maintaining lung health exceeds two hours per day. Inhaled intravenous or oral antibiotic treatments are used to control infections. Persistent infections eventually destroy the lungs, and while lung transplantation may help end-stage CF patients, the extended median life expectancy is only 34 months following a lung transplant (*CADTH Common Drug Review annotation: A recent study based on data from the Canadian CF database reported median survival of 10 years among patients with a lung transplant*).[27]

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

3. Related Information About the Drug Being Reviewed

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

Although they have no experience with Kalydeco, a number of people living with CF, as well as their family members, have indicated that they expect it will improve lung function, weight gain and, in many cases, help to avoid the need for lung transplantation. One mother of two children with CF stated that having access to Kalydeco will give her children a chance to live a fuller life in terms of attending university, finding their dream job, and starting a family.

Those who have been on Kalydeco, either through clinical trials or private insurance, have reported improvements in CF symptoms, energy levels, lung function, and weight gain. The improvements in health have also led to better quality of life and ability to function normally.

4. Additional Information

Since Kalydeco was approved for use in Canada, individuals aged six years and older with the G551D mutation have access to Kalydeco through public drug plans in Ontario, Alberta, Saskatchewan, Nova Scotia, Manitoba, New Brunswick, Yukon, and British Columbia. As of the date of this submission, the drug has received a positive recommendation by the CADTH Common Drug Review for use in nine additional gating mutations for individuals aged six and older, and is currently subject to the pan-Canadian Pharmaceutical Alliance negotiations.

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:	June 8, 2015
Alerts:	Weekly search updates until November 18, 2015.
Study types:	No search filters were applied
Limits:	No language or date limits 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
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
.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-SEARCH DATABASE	
#	**Searches**
1	(Kalydeco* or ivacaftor* or UNII1Y740ILL1Z 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 use oemezd
9	4 or 8
10	9 not conference abstract.pt.
11	remove duplicates from 10

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:	June 2, 2015
Keywords:	Drug name, Indication
Limits:	No language or date 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
Clinical Study Report: VX11-770-112. A phase 3, two-arm, rollover study to evaluate the safety of long-term Ivacaftor treatment in subjects 6 years of age and older with cystic fibrosis and a non-G551D CFTR mutation [**CONFIDENTIAL** internal manufacturer's report]. Version 4.0. Boston (MA): Vertex Pharmaceuticals Incorporated; 2014 Feb 13.	Wrong study design (not randomized controlled trial)
De Boeck K, Munck A, Walker S, Faro A, Hiatt P, Gilmartin G, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. J Cyst Fibros. 2014 Dec;13(6):674-80.	Wrong population

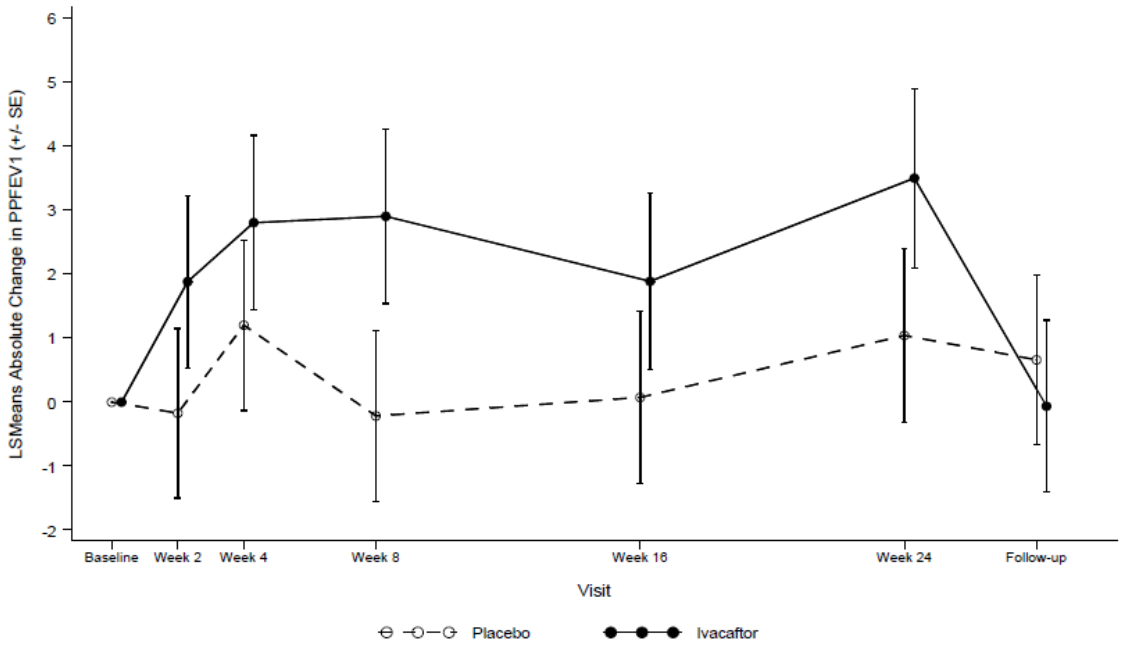
APPENDIX 4: DETAILED OUTCOME DATA

TABLE 9: SUBGROUP ANALYSIS OF ppFEV$_1$ BY BASELINE PULMONARY FUNCTION: KONDUCT TRIAL

Outcome: ppFEV$_1$	Overall Population (FAS)		Adult Subgroup (Aged ≥ 18 Years)[a]	
Subgroup	**Placebo**	**Ivacaftor**	**Placebo**	**Ivacaftor**
Baseline ppFEV$_1$ < 70%	**N = 15**	**N = 13**	**N = 15**	**N = 13**
Absolute change from baseline to week 24, LS mean (SE)	0.4 (2.0)	4.5 (2.2)	0.4 (2.0)	4.5 (2.2)
Treatment difference ivacaftor versus placebo (95% CI), *P* value	4.0 (–2.1 to 10.1) *P* = 0.19		4.0 (–2.1 to 10.1) *P* = 0.18	
Baseline ppFEV$_1$ ≥ 70% and ≤ 90%	**N = 14**	**N = 14**	**N = 11**	**N = 10**
Absolute change from baseline to week 24, LS mean (SE)	0.2 (1.6)	2.8 (1.7)	–1.3 (1.5)	5.1 (1.6)
Treatment difference ivacaftor versus placebo (95% CI), *P* value	2.6 (–2.3 to 7.5) *P* = 0.28		6.4 (1.8 to 11.1) *P* = 0.009	
Baseline ppFEV$_1$ > 90%	**N = 6**	**N = 7**	**N = 0**	**N = 1**
Absolute change from baseline to week 24, LS mean (SE)	2.2 (1.8)	–2.1 (1.6)	--	--
Treatment difference ivacaftor versus placebo (95% CI), *P* value	–4.3 (–9.9 to 1.3) *P* = 0.12		--	

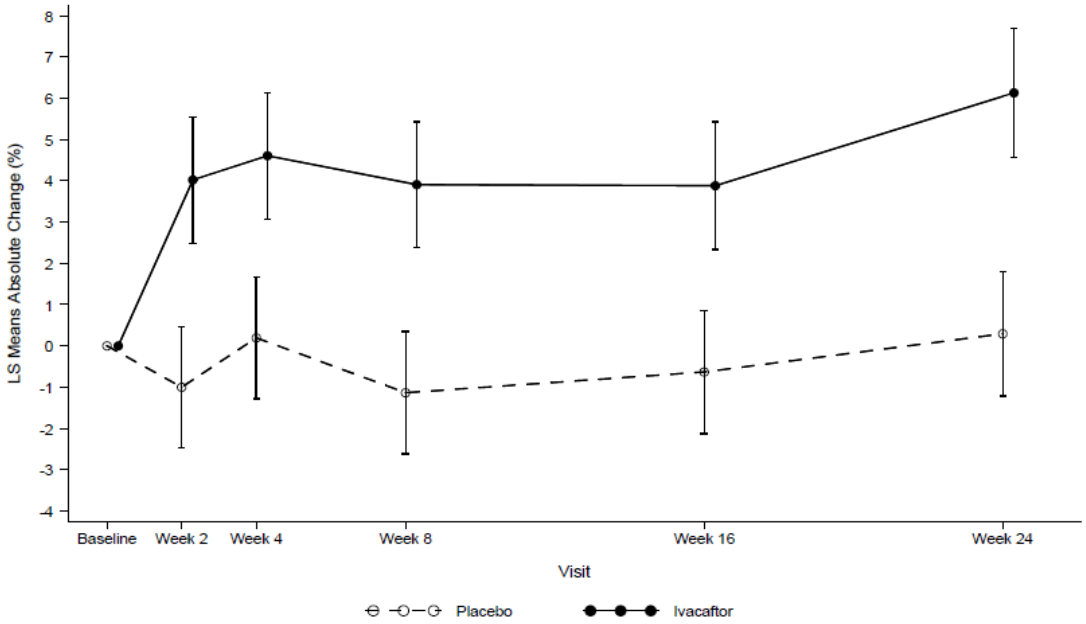
CI = confidence interval; FAS = full analysis set; LS = least-squares; NR = not reported; ppFEV$_1$ = per cent predicted forced expiratory volume in 1 second; SE = standard error.
[a] Post hoc subgroup analysis.
Source: Clinical Study Report.[11]

FIGURE 2: ABSOLUTE CHANGE IN ppFEV$_1$ FROM BASELINE TO FOLLOW-UP VISIT (FAS): KONDUCT TRIAL



FAS = full analysis set; LS = least-squares; ppFEV$_1$ = per cent predicted forced expiratory volume in 1 second; SE = standard error.
Source: Clinical Study Report,[11] pg. 1544.

FIGURE 3: ABSOLUTE CHANGE IN ppFEV$_1$ FROM BASELINE TO WEEK 24 (ADULT SUBGROUP): KONDUCT TRIAL



LS = least-squares; ppFEV$_1$ = per cent predicted forced expiratory volume in 1 second.
Source: Clinical Study Report,[11] pg. 1551.

TABLE 10: RESPONDER ANALYSIS OF ABSOLUTE CHANGE THROUGH WEEK 24 IN ppFEV$_1$: KONDUCT TRIAL

Category	Overall Population (FAS)		Adults Subgroup (Aged ≥ 18 Years)	
	Placebo N = 35 n (%)	Ivacaftor N = 34 n (%)	Placebo N = 26 n (%)	Ivacaftor N = 24 n (%)
≥ 5%	7 (20)	13 (38)	[redacted]	[redacted]
< 5%	28 (80)	21 (62)	[redacted]	[redacted]
≥ 10%	2 (6)	5 (15)	[redacted]	[redacted]
< 10%	33 (94)	29 (85)	[redacted]	[redacted]

FAS = full analysis set; ppFEV$_1$ = per cent predicted forced expiratory volume in 1 second.
Source: Clinical Study Report.[11]

FIGURE 4: TIME TO FIRST PULMONARY EXACERBATION: ADULT SUBGROUP IN KONDUCT TRIAL

Figure redacted at the request of the manufacturer

Source: Clinical Study Report.[11]

TABLE 11: MAXIMUM ON-TREATMENT LIVER FUNCTION TEST RESULTS (KONDUCT TRIAL)

Maximum On-Treatment Result	Liver Function Test	Placebo (N = 35) n (%)	Ivacaftor (N = 34) n (%)
≤ 2 × ULN	ALT (U/L) AST (U/L) Total bilirubin (µmol/L)	33 (94.3) 35 (100.0) 35 (100.0)	31 (91.2) 33 (97.1) 34 (100.0)
> 2 × ULN to ≤ 3 × ULN	ALT (U/L) AST (U/L) Total bilirubin (µmol/L)	1 (2.9) 0 0	2 (5.9) 1 (2.9) 0
> 3 × ULN to ≤ 5 × ULN	ALT (U/L) AST (U/L) Total bilirubin (µmol/L)	1 (2.9) 0 0	1 (2.9) 0 0
> 5 × ULN to ≤ 8 × ULN	ALT (U/L) AST (U/L) Total bilirubin (µmol/L)	0 0 0	0 0 0
> 8 × ULN	ALT (U/L) AST (U/L) Total bilirubin (µmol/L)	0 0 0	0 0 0

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal.
Notes: Baseline is defined as the most recent measurement before intake of the first dose of the study drug. The result categorized is the maximum of all post-baseline liver function test results occurring on or before the week 24 visit.
Source: Table 14.3.4.10, Clinical Study Report pg. 252.[11]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

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

- Forced expiratory volume in one second (FEV_1)
- Cystic Fibrosis Questionnaire – Revised (CFQ-R).

Findings

Forced Expiratory Volume in One Second

FEV_1 is the maximal amount of air forcefully exhaled in one second, expressed in litres.[28] The measured volume is converted to a percentage of predicted normal value, which is adjusted based on age, sex, and body composition.[28] FEV_1 is used to establish the severity of lung disease (normal or mild pulmonary dysfunction, > 70% predicted; moderate dysfunction, 40% to 69% predicted; and severe dysfunction, < 40% predicted), tracking changes in lung function over time, and in evaluating the effectiveness of therapeutic interventions in cystic fibrosis (CF).[28,29]

FEV_1 is a commonly used end point for clinical trials of obstructive lung diseases including CF[30] 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.[29] FEV_1 has been shown to relate to morbidity, disease progression, and mortality in CF, making it a meaningful surrogate marker for survival.[30]

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

- The manoeuvre required to assess FEV_1 is highly dependent on patient co-operation and effort:
  - The test (spirometry) should be repeated at least three times to ensure reproducibility;[28]
  - Spirometry can be used only on children old enough to comprehend and follow the instructions given (aged six years or older), and only on patients who are able to understand and follow instructions;[29,30] and
  - FEV_1 can generally only be underestimated. The only exception in which FEV_1 can be overestimated is in individuals with some diseases where a softer exhalation can reduce the spasm or collapse of lung tissue, thereby artificially elevating the measure.
- FEV_1 decline is only meaningful over time and is subject to seasonal and environmental effects.[30]
- There are no published data on the magnitude of change in FEV_1 that are clinically meaningful.[30]
- CF is a multi-organ disease and FEV_1 measures only lung health.[30]
- FEV_1 improvement has a ceiling effect for patients with mild lung impairment.[30]
- There are no published MCIDs for FEV_1 in patients with CF.

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.[29]

Cystic Fibrosis Questionnaire – Revised

The CFQ-R is a disease-specific quality-of-life (QoL) instrument designed for patients with CF, comprising age-appropriate versions for children aged six to 13 years (CFQ-C) and their parents (who serve as a proxy for their child; CFQ-P), and individuals aged 14 years or older (CFQ-14).[31] 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 quality of life. The scales are designed to measure functioning during the two-week period prior to administration of the CFQ-R.[21]

Several studies have evaluated the validity and reliability of the CFQ-R questionnaire.[18-20] Recently, Quittner et al.[18] 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-R was sensitive to changes in QoL associated with increasing disease severity (based on pulmonary function, FEV_1); however, this analysis was limited, as the CFQ-C had less variability in disease severity because few school-age children had a FEV_1 < 70% predicted. Quittner et al.[18] also reported fair to moderate agreement between the child and parent versions on all scales (intraclass correlation coefficient range, 0.26 to 0.56); however, stronger agreement was found on domains that measured more observable signs and symptoms, such as physical functioning, eating problems, and respiratory symptoms. There was fair to moderate convergence between CFQ-R scales and health outcomes, including per cent predicted FEV_1 ($ppFEV_1$; correlation range, 0.25 to 0.51), number of pulmonary exacerbations treated with intravenous antibiotics (range, –0.23 to –0.35), and body mass index (BMI) (range, 0.22 to 0.44). The strongest correlations were demonstrated for the physical functioning and respiratory domains with $ppFEV_1$ (range, 0.33 to 0.51 and 0.32 to 0.42, respectively) and for the weight scale and BMI (r = 0.42 and 0.44 on the CFQ-P and CFQ-14, respectively). Overall, the correlations were lower for the CFQ-C and CFQ-P versus the CFQ-14. Test–retest reliability was assessed previously (repeat administration over 14 days) and intraclass correlation coefficients were estimated to range from 0.45 to 0.90 on all scales.[19]

A previous study[19] also showed the CFQ-R correlated well with the Short-Form (36) Health Survey (SF-36). Correlations were high (r = 0.42 to 0.57) among 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 *Pseudomonas aeruginosa* airway infection; the other with patients with exacerbation of CF and chronic *P. aeruginosa* airway infection.[21] Both anchor-based and distribution-based methods were used. The MCID, or the smallest change a patient could detect in terms of changes in respiratory symptoms, for patients with stable disease was determined to be 4.0, and for patients with exacerbation, 8.5.[21]

The main limitations of the CFQ-R are ceiling effects for certain scales (notably the eating problems scale), potential difficulty for patients to understand some of the items (e.g., CFQ-R-Respiratory, item "trouble breathing"), and concerns that a patient may not be able to distinguish between some of the response items on the scale (e.g., response choices such as "somewhat" versus "a little").[18,30]

Conclusion

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

APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION STUDY

Aim

To summarize interim data (12 weeks) from study 112, a rollover study of ivacaftor in patients with cystic fibrosis (CF) and a non-G551D cystic fibrosis transmembrane conductance regulator (CFTR) mutation.

Findings

Study 112[32] is an ongoing phase 3, two-arm, open-label, rollover study to evaluate the safety of long-term ivacaftor treatment in patients aged six years and older with CF and a non-G551D CFTR mutation. The study included patients with CF who had previously been enrolled in KONDUCT (study 110, enrolling patients with R117H-CFTR mutation), study 111 (patients with a non-G551D-CFTR gating mutation), or study 113 (patients with phenotypic or molecular evidence of residual CFTR function). The primary objective of study 112 is to evaluate the safety of long-term ivacaftor treatment in patients with CF, assessed by the risk of serious adverse events. The secondary objective is to evaluate the efficacy of long-term ivacaftor treatment in patients with CF, measured by spirometry (per cent predicted forced expiry volume in one second [ppFEV$_1$]), sweat chloride test, and the respiratory domain of the Cystic Fibrosis Questionnaire – Revised (CFQ-R).

Study 112 includes two arms: an ivacaftor arm, in which patients receive ivacaftor 150 mg every 12 hours, and an observational arm, in which patients do not receive the study drug. The ivacaftor arm of study 112 includes those patients who:

- completed their assigned study drug treatment duration in study 110 or study 111
- completed all study-related treatments through the follow-up visit in study 113 and met at least one of the study 113 responder criteria during the eight-week open-label period of that study.

The observational arm of study 112 includes patients from study 110 and study 111 who

- prematurely discontinued study drug treatment and received at least four weeks of treatment in the previous ivacaftor study;
- completed the previous study and enrolled in the observational arm; or
- completed the previous study but did not meet the inclusion criteria for the ivacaftor arm.

The interim analyses included only patients from study 110 who enrolled in the ivacaftor arm of study 112. The ivacaftor arm was further divided into ivacaftor/ivacaftor group (i.e., patients who received ivacaftor in study 110 and in study 112), and placebo/ivacaftor group (i.e., patients who received placebo in study 110 and ivacaftor in study 112). Of the 69 patients enrolled in study 110, 65 enrolled in the ivacaftor arm of study 112, two enrolled in the observational arm of study 112, and two did not enroll in study 112 due to early discontinuation of treatment in study 110. Of the 65 patients, 64 completed at least 12 weeks of treatment in study 112, and one patient (in the ivacaftor/ivacaftor group) discontinued due to leaving the country.

The full analysis set (FAS) for this interim analysis included the 65 patients from study 110 who enrolled in the ivacaftor arm of study 112 and received at least one dose of ivacaftor in study 112: 30 patients in the ivacaftor/ivacaftor group and 35 patients in the placebo/ivacaftor group. The safety follow-up visit for study 110 was used as the baseline visit for study 112. Demographic characteristics for the FAS population are summarized in Table 12. The two patients enrolled in the observational arm of study 112 were included in the safety set.

TABLE 12: DEMOGRAPHIC CHARACTERISTICS (FULL ANALYSIS SET) IN STUDY 112

Variable	Placebo/Ivacaftor N = 35	Ivacaftor/Ivacaftor N = 30	Overall N = 65
Male, n (%)	[redacted]	[redacted]	[redacted]
Race: White, n (%)	[redacted]	[redacted]	[redacted]
Ethnicity: Non-Hispanic or Latino, n (%)	[redacted]	[redacted]	[redacted]
Age (at study 110 baseline), mean (SD)	[redacted]	[redacted]	[redacted]
Age group (years, at study 110 baseline), n (%)			
6 to 11	8 (22.9)	7 (23.3)	15 (23.1)
12 to 17	[redacted]	[redacted]	[redacted]
≥ 18	[redacted]	[redacted]	[redacted]

SD = standard deviation.
Source: Clinical Study Report.[32]

Between-group statistical testing was not performed for efficacy and safety outcomes. A descriptive summary was provided for serious adverse events that occurred from day 1 of study 112 through week 12. A total of eight patients reported 12 serious adverse events during this period; all eight patients reported nine infective pulmonary exacerbations of CF, of which six cases occurred in the ivacaftor/ivacaftor group. One patient (from the placebo/ivacaftor group) reported angioedema and urticaria, and another patient (from ivacaftor/ivacaftor group) reported influenza in addition to pulmonary exacerbation.

Mean absolute changes from study 112 baseline in $ppFEV_1$, CFQ-R respiratory domain score, and sweat chloride are presented in Table 13. For the FAS and for the ≥ 18 years subgroup, statistically significant increases in $ppFEV_1$ occurred for the overall population, for the placebo/ivacaftor group, and for the ivacaftor/ivacaftor group. For patients aged six to 11 years, the mean increase in $ppFEV_1$ was not statistically significant.

Decreases in sweat chloride values from baseline were observed at week 2 for the FAS and for patients in both age subgroups. For the FAS and for the ≥ 18 years subgroup, absolute decreases from baseline sweat chloride values were slightly greater in the placebo/ivacaftor group than in the ivacaftor/ivacaftor group. For the six to 11 years subgroup, comparable decreases from baseline sweat chloride values were observed for the placebo/ivacaftor and ivacaftor/ivacaftor groups. It was not reported whether the changes from baseline in sweat chloride levels were statistically significant.

The overall CFQ-R respiratory domain scores increased from baseline at weeks 2 and 12 for the FAS and for patients in both age subgroups; these increases were all greater than the defined minimal clinically important difference (MCID) of 4 points in absolute terms. However, statistical testing was not performed for the observed changes from baseline. The overall increase in pooled CFQ-R respiratory domain scores for patients six to 11 years of age was greater than the increase observed for the FAS and for the ≥ 18 years subgroup at the two study visits, although this was driven by one patient who had a substantial increase in FEV_1 following resolution of a pulmonary exacerbation in study 110. For all age subgroups, increases in CFQ-R respiratory domain scores were lower at weeks 2 and 12 for patients in the placebo/ivacaftor group than for those in the ivacaftor/ivacaftor group.

TABLE 13: SUMMARY OF KEY EFFICACY OUTCOMES FROM STUDY 112

	Placebo/Ivacaftor, N = 35			Ivacaftor/Ivacaftor, N = 30			Overall, N =65		
	Study 112 Baseline	Mean Change At 2 Weeks	Mean Change At 12 Weeks	Study 112 Baseline	Mean Change At 2 Weeks	Mean Change At 12 Weeks	Study 112 Baseline	Mean Change At 2 Weeks	Mean Change At 12 Weeks
% Predicted FEV_1 (SD) FAS									
FAS	71.00 (21.5) (N = 35)	3.24 (6.7); P^a = 0.007; (N = 35)	5.00 (7.7); P^a = 0.0005; (N = 35)	72.69 (19.5) (N = 30)	4.46 (9.4); P^a = 0.014 (N = 30)	6.04 (10.4); P^a = 0.006 (N = 27)	71.78 (20.4) (N = 65)	3.80 (8.0); P^a = 0.0003 (N = 65)	5.45 (8.9); P^a < 0.0001 (N = 62)
6 to 11 years	97.54 (11.8) (N = 8)	–1.82; P^a = 0.035 (N = 8)	3.58; P^a = 0.2334 (N = 8)	85.84 (22.1) (N = 7)	9.41; P^a = 0.2074 (N = 7)	9.78; P^a = 0.1978 (N = 7)	92.08 (17.8) (N = 15)	3.45; P^a = 0.3246 (N = 15)	6.47; P^a = 0.0806 (N = 15)
≥ 18 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sweat chloride, mmol/L (SD)[b], FAS									
FAS	65.38 (19.51) (N = 33)	–20.94 (9.07) (N = 33)	Not assessed[c]	55.31 (18.14) (N = 26)	–17.21 (12.29) (N = 26)	Not assessed[c]	60.94 (19.42) (N = 59)	–19.30 (10.68) (N = 59)	Not assessed[c]
6 to 11 years	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
≥ 18 years	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
Pooled CFQ-R respiratory domain score (SD)[b], FAS									
FAS	[redacted]	[redacted]	8.17 (13.99) (N = 35)	[redacted]	[redacted]	15.71 (21.42) (N = 29)	[redacted]	[redacted]	11.59 (17.99) (N = 64)
6 to 11 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 18 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CFQ-R = Cystic Fibrosis Questionnaire – Revised; FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second; SD = standard deviation.

[a] *P* value for the difference from baseline (one-sample t test).

[b] Statistical testing for the difference from baseline was not performed.

[c] Sweat chloride was collected only at the following study visits: day 1 and week 2, 24, 48, and 104 visits.

Source: Study 112 Clinical Study Report.[32]

Limitations

The primary limitations in study 112 are the lack of an adequate control group and open-label design. Efficacy results were not tested for statistical significance. Furthermore, these results, specifically self-reported health-related quality of life, should be interpreted with caution given the open-label design and patient's awareness of treatment.

Conclusion

Study 112 is an ongoing open-label study that enrolled patients with non-G551D-CFTR gating mutation from study 110 (KONDUCT), study 111, and study 113. The interim analysis contained only patients originating from the KONDUCT trial; hence, the results are relevant to the indication under review.

The overall safety profile observed during the interim week 12 analysis of study 112 was generally consistent with that seen during study 110. There were no new safety concerns with extended use of ivacaftor in study 112.

Overall, the efficacy results through 12 weeks in study 112 were supportive of those observed during study 110. Improvements in ppFEV$_1$, CFQ-R respiratory domain, and sweat chloride were sustained during study 112.

APPENDIX 7: SUMMARY OF R117H MUTATION TESTING

Aim

To summarize the use of R117H mutation testing in patients with cystic fibrosis (CF).

Findings

Description and Clinical Utility of R117H Mutation

R117H is a missense mutation that results in the replacement of an arginine residue (i.e., "R") at position 117 of the cystic fibrosis transmembrane conductance regulator (CFTR) gene with a histidine residue (i.e., "H").[12] The R117H mutation is associated with a primary gating defect and residual chloride channel conductance function.[12] In vitro studies revealed that the channel open probability (or gating) of CFTR with R117H was reduced to 28% of normal and that CFTR-mediated chloride transport (conductance function) was 86% of normal.[12] R117H is classified as a low-risk CFTR genotype (class IV).[6] With class IV mutations, the protein is produced and correctly localized to the cell surface. However, the rate of ion flow and the duration of channel opening are reduced compared with normal CFTR function.[33] The R117H-CFTR poly-T tract occurs as one of three variants (5T, 7T, or 9T).[34-36] R117H-5T results in a more severe disease phenotype than R117H-7T, and R117H-9T is highly unlikely to cause disease.[11] R117H-5T generally results in pancreatic sufficient CF, while R117H-7T may result in a mild form of CF, obstructive azoospermia, or no disease at all.[5] Therefore, when R117H is detected, it is important to establish the 5T or 7T status.[5] However, genotype–phenotype correlations are imprecise and should not be used clinically in predicting lung involvement or survival in patients with R117H mutation .[37]

R117H is a relatively frequent mutation in CF patients globally[5] and is the most common class IV mutation in Caucasians.[33] R117H –CFTR mutation is present in approximately 3% of CF patients.[3,38] In newborn screening programs, up to 7% of newborns with an elevated immunoreactive trypsinogen test and two mutations were compound heterozygous for R117H-7T and a CF-causing CFTR mutation.[5,39] These children may have no major signs of CF in their first years of life, but they may develop manifestations of CF disease in adulthood.[5,40] Based on data from the Canadian CF Patient Data Registry, the manufacturer has estimated there are 36 to 56 adult CF patients with the R117H mutation in Canada,[12] although this may be an underestimate, as not all patients with R117H and CFTR-related manifestations meet the diagnostic criteria for CF.

Description of R117H Mutation Testing

DNA sequencing is considered the "gold standard" for DNA-based mutation testing.[37] However, for clinical laboratory settings, routine DNA sequencing is currently not practical or cost-effective in most centres for identifying CFTR gene mutations, with more than 1,800 reported mutations in the CF gene.[38,41] Hence, the American College of Medical Genetics and Genomics (ACMG) and the American Congress of Obstetricians and Gynecologists (ACOG) recommend testing patients diagnosed with, or at risk for, CF for the 23 most common CF mutations (including the R117H mutation), representing an allele frequency of ≥ 0.1% in the general population.[37,42] The new ACMG panel of 23 mutations accounts for 94.04% of detectable mutations.[37] Several CFTR mutation testing systems have been developed to detect the most frequently occurring CF gene mutations. These systems use multiplex polymerase chain reaction (PCR)-based hybridization (with mutation-specific oligonucleotide probes) to detect the ACMG/ACOG 23 mutations. Some testing systems test for extra mutations beyond the minimum 23 that may be of clinical interest;[41] one panel included 106 mutations that account for approximately 91% of CF genes in a Northern European Caucasian population.[43]

Various procedures for molecular diagnosis of CF are reported in the literature, including allele-specific oligonucleotide dot-blot, reverse dot-blot, amplification refractory mutation system (ARMS) , and oligonucleotide ligation assay (OLA)-PCR.[44] Commercially available CF testing platforms include the eSensor Cystic Fibrosis Carrier Detection System, CF v3.0 OLA analyte-specific reagent (ASR), CFTR InPlex ASR, Signature CF 2.0 ASR, INNO-LiPA CFTR 35, CF Gold 1.0, Tag-It CF 40 + 4, CF eMAP/Bead Chip, and Invader.[44] Among the above-mentioned platforms, only Tag-It CF 40 + 4 is used in Canada (Tm Biosciences, Toronto, Ontario, Canada).[44] In one study,[44] Johnson et al. evaluated five CFTR testing platforms: the eSensor Cystic Fibrosis Carrier Detection System CFTR, InPlex ASR; CF v3.0 OLA ASR; Signature CF 2.0 ASR; and Tag-It mutation detection kit for CFTR 40 + 4. The authors subjected each platform to seven independent amplifications and runs with the same core set of 150 DNA samples (representing the ACMG- and ACOG-recommended panel of 23 CFTR mutations and normal samples) to assess the performance of each platform. Of the panels evaluated, InPlex tested for the greatest number of mutations (42 in total). All platforms demonstrated good specificity and sensitivity (100% concordance) and acceptable test repeat rates (all ≤ 0.7%). The start-to-finish time and hands-on time were similar across all platforms, although the InPlex system required the least time in both categories. Likewise, all were considered relatively easy to use (based on number of steps, tolerances within those steps, and number of sample transfers) and again the InPlex system was considered the better platform. All of the platforms require specialized instrumentation. With the exception of the eSensor, additional tests can be run using the same instrumentation. In addition, three platforms — Tag-It, Signature, and OLA — are open platforms and allow development of custom tests. It is perhaps not surprising that there were few differences in performance between the platforms evaluated by Johnson et al.,[44] as the manufacturers likely follow the ACMG and ACOG standards and guidelines for CFTR tests, which specify the type of test that should be used (i.e., PCR-based) and criteria for the analytical and clinical validity of tests.[37]

All patients included in the KONDUCT study had the R117H mutation on at least one CFTR allele. CFTR genotype was screened and confirmed by Quest Diagnostics, California, US. R117H allele poly-T tract was determined by Arup Laboratories, Utah, US. However, details of the platforms for genetic testing were not described in the Clinical Study Report.[11] All patients enrolled in this study would have had the R117H-5T or R117H-7T alleles because the study entry criteria required that patients have CF, as evidenced by sinopulmonary disease and a sweat chloride ≥ 60 mmol/L, or two CF-causing mutations.[11]

Current Canadian Practice Regarding R117H Testing

The Canadian College of Medical Geneticists (CCMG) committee endorsed that CFTR mutation testing may be indicated for individuals or families at increased risk of CF due to considerations of family history or clinical manifestations.[45] The clinical expert consulted for this review confirmed that R117H mutation testing is part of the standard panel of mutations that CF patients are screened for. However, in terms of testing systems or platforms, no specific R117H–CFTR mutation testing recommendation was identified in the CCMG guideline (2011).[45] The limited search of the published and grey literature for this review revealed that the Tag-It CF 40 + 4 platform is used in Canada, but there was very little publicly available information on many aspects of CF mutation testing in Canada, including what tests are used, their performance, and issues concerning access, availability, and the cost of the tests. According to CF Canada, 97% of Canadian CF patients have had genotyping performed.[26]

Conclusion

DNA sequencing is the gold standard for CFTR mutation testing. However, it is not practical or cost-effective in routine clinical practice. The ACMG/ACOG recommendation is to test for the 23 most common mutations including the R117H mutation in people with, or at risk for, CF. All CFTR mutation tests use multiplex PCR as the DNA assay method. In terms of the CFTR mutation testing system or platforms, no recommendation was identified in the CCMG guideline (2011). Based on the limited literature search for this review, the Tag-It CF 40 + 4 is the only platform used in Canada. There was very little published or publicly available information on many aspects of the CF mutation tests used in Canada, including confirmation of what tests are used, their performance, and issues concerning access, availability, and the cost of the tests.

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