LUMACAFTOR/IVACAFTOR (ORKAMBI — VERTEX PHARMACEUTICALS (CANADA) INCORPORATED)
Indication: Cystic fibrosis, F508del-cystic fibrosis transmembrane conductance regulator gene mutation in patients aged six years and older.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that lumacaftor/ivacaftor not be reimbursed for the treatment of cystic fibrosis in patients aged six years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene.
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**LUMACAFTOR/IVACAFTOR (ORKAMBI — VERTEX PHARMACEUTICALS (CANADA) INCORPORATED)**

Indication: Cystic Fibrosis, F508del-cystic fibrosis transmembrane conductance regulator gene mutation in patients aged six years and older.

**Recommendation:**

The CADTH Canadian Drug Expert Committee (CDEC) recommends that lumacaftor/ivacaftor (LUM/IVA) not be reimbursed for the treatment of cystic fibrosis (CF) in patients aged six years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

**Reasons for the Recommendation**

1. Although two double-blind, randomized controlled trials (RCTs) (TRAFFIC [N = 559] and TRANSPORT [N = 563]) demonstrated that treatment with LUM 400 mg every 12 hours/IVA 250 mg every 12 hours (L400/IVA) was associated with statistically significant absolute improvements in per cent predicted forced expiratory volume in one second (ppFEV1) compared with placebo, the magnitude of improvement (2.6% to 3.0%) was of uncertain clinical significance. In addition, responder analyses demonstrated that the majority of L400/IVA-treated patients (73%) failed to achieve an absolute improvement of at least 5% in ppFEV1. The manufacturer conducted a matched-registry cohort analysis that suggested the slope of decline in lung function was reduced in patients who were treated with L400/IVA in the PROGRESS study compared with a matched cohort of patients from a US registry (−1.33% versus −2.29% per year over a two-year period). Due to limitations in the analysis, concerns regarding the comparability of the patients from the clinical trials and those from the registry, and issues regarding the generalizability of US registry patients with Canadian patients with CF, it is uncertain if treatment with L400/IVA would have a similar impact on the rate of lung function decline in Canadian patients.

2. L400/IVA was associated with a lower rate of pulmonary exacerbations compared with placebo after 24 weeks of treatment in the TRAFFIC and TRANSPORT trials; however, the results could not be considered statistically significant because the hierarchical statistical analysis plan used in both studies failed to demonstrate statistical significance at a higher order comparison. As well, the data for pulmonary exacerbations were limited by the relatively short duration of the trials and the absence of independent adjudication of exacerbation events.

3. The included RCTs failed to consistently demonstrate that treatment with L400/IVA is associated with statistically significant improvements in body mass index (BMI), body weight, and height in patients at least 12 years of age. Although a statistically significant improvement in BMI was reported in TRANSPORT, the magnitude of improvement was of uncertain clinical significance. In patients aged six years to 11 years, treatment with LUM 200 mg every 12 hours/IVA 250 mg every 12 hours (L200/IVA) was not associated with statistically significant improvements in nutritional BMI, BMI-for-age z score, weight, weight-for-age z score, height, or height-for-age z score.

4. In patients aged six years to 11 years of age, L200/IVA was associated with a statistically significant improvement in lung clearance index 2.5% (LCI2.5) compared with placebo after 24 weeks of treatment (absolute reduction of −1.09). The clinical significance of this finding is uncertain as the minimally clinically important difference (MCID) has not been established for this end point, its validity as a surrogate marker for respiratory exacerbations is unknown, and it is not currently used in Canadian clinical practice. Treatment with L200/IVA resulted in an improvement in ppFEV1 after 24 weeks of treatment compared with placebo (2.4%); however, the clinical significance of this result is uncertain. Treatment with L200/IVA was not associated with a statistically significant improvement in the rate of pulmonary exacerbations in patients six years to 11 years of age.

5. There were no statistically significant improvements in health-related quality of life using the Cystic Fibrosis Questionnaire – Revised (CFQ-R) respiratory domain scores with L400/IVA or L200/IVA versus placebo at 24 weeks.

**Discussion Points:**

- Potential improvements in lung function can be evaluated based on short-term changes from baseline (e.g., absolute or relative change from baseline in ppFEV1 or LCI2.5 as measured in the clinical trials) or long-term changes evaluating the impact of an intervention on the course of CF (e.g., slope of decline as modelled in PROGRESS and the matched cohort...
study). When considering lung function measurements in a chronic condition such as CF, the ability of a treatment such as LUM/IVA to result in longer-term changes is generally considered to be more clinically relevant than acute changes in ppFEV₁.

- CF is a life-threatening, seriously debilitating disease that is chronic in nature. There are approximately 2,000 patients in Canada with CF who are homozygous for the F508del mutation in the CFTR gene. CDEC discussed the unmet therapeutic need for patients who are homozygous for the F508del mutation in the CFTR gene and concluded that there is insufficient evidence to conclude that treatment with LUM/IVA will address the unmet need and improve long-term outcomes for these patients.

- CDEC considered the recommendations from Cystic Fibrosis Canada’s Physician Panel and discussed LUM/IVA’s potential place in therapy with clinical specialists who have experience in the diagnosis and management of children and adults living with CF. The committee heard from some of the specialists that there may be a place in therapy for patients who are at risk for rapid deterioration. This was discussed at length and it was noted that these patients were excluded from the RCTs and that clinical criteria are not currently available to facilitate the identification of such patients in clinical practice. In addition, the absence of established thresholds for clinically significant changes in the clinical parameters that are routinely measured in clinical practice (most notably ppFEV₁) and variability in the occurrence and timing of pulmonary exacerbations make it challenging to define discontinuation criteria for LUM/IVA that could be implemented in a consistent manner across the CADTH Common Drug Review (CDR)–participating drug plans.

- CDEC discussed the potential for cumulative health benefits from relatively modest improvements in most of the study outcomes with LUM/IVA treatment. CDEC noted that the aforementioned limitations in the designs (especially the relatively short duration of follow-up for a chronic condition) and limitations in the analyses of the studies precluded drawing conclusions with respect to the overall health benefits of LUM/IVA.

- CDEC noted the following important gaps in the evidence for LUM/IVA:
  - There are no RCTs designed to examine the effect of LUM/IVA treatment on the rate of decline in lung function or the rate of pulmonary exacerbations that have been adjudicated by blinded experts during at least one year of follow-up. A full year is needed to understand the effects of seasonal variation on exacerbations.
  - Evidence for use in patients with severe lung disease is limited to a single, short-term, uncontrolled study involving a small number of patients (N = 46), and no studies were conducted to examine the effect of LUM/IVA on patients with rapidly progressive disease.
  - There are no studies that have examined the effect of LUM/IVA on the need for lung transplantation, or survival.

**Background:**

LUM/IVA is a fixed-dose combination tablet containing 100 mg (for patients aged 6 years to 11 years) or 200 mg (for patients aged 12 years and older) LUM and 125 mg IVA. It is indicated for the treatment of CF in patients aged six years and older who are homozygous for the F508del mutation in the CFTR gene. The product monograph recommends a dose of two tablets taken orally every 12 hours with fat-containing food.

**Submission History:**

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

**Summary of CDEC Considerations:**

The committee considered the following information prepared by CADTH: a systematic review of RCTs and pivotal studies, a review of extension phase studies, a single-arm study conducted in patients with severe lung disease, and a critique of the manufacturer’s pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with CF and patient group–submitted information about outcomes and issues important to patients and caregivers.
Patient Input Information

Two patient groups, Cystic Fibrosis Canada (CF Canada) and the Cystic Fibrosis Treatment Society, responded to CADTH’s call for patient input. Patient perspectives were obtained from a national survey conducted in January 2018 and February 2018, testimonials from patients with CF and their families, CF Canada publications (e.g., 2016 CF Canada Registry Annual Data Report), and data from SickKids hospital and Genome Canada. The following is a summary of key input from the perspective of the patient groups:

- Managing CF requires a demanding treatment routine with regular visits to specialized CF clinics. CF treatments, CF-related infections, and hospitalizations take a toll on patients’ emotional stamina and have a significant impact on their day-to-day quality of life, affecting life decisions that include education, career, travel, relationships, and family planning. Treatments that may consume two to seven hours per day and may include hospitalizations disrupt family routines.

- Caregivers are faced with significant emotional, psychological, physical, and financial burdens. They may feel helpless and devastated, watching their loved ones cope with a life-threatening disease. Social activities and employment can be significantly affected in order to accommodate the treatment of a loved one with CF. It was also noted that limited access to new treatments (e.g., LUM/IVA) can have a negative impact on the mental health and well-being of patients and caregivers, due to perceptions of unfair access to what could be a life-altering drug.

- Patients indicated that there is a need for additional CF treatments that can prolong their lives, improve their quality of life, allow them to work, study, and participate more fully in social and physical activities, reduce the need for hospitalizations, avoid the need for lung transplantation, help them gain weight, and reduce the frequency and severity of pulmonary exacerbations. The majority of the 68 patients and caregivers who described their own or their loved ones’ experience with LUM/IVA reported improved lung function, a reduced rate of exacerbations, and improved nutritional status, and emphasized the cumulative positive effect on their quality of life.

- Patients are willing to tolerate adverse effects if they believe the potential benefits outweigh the possible side effects. The patient groups noted that some patients reported uncomfortable side effects, including tightness in their chest when starting treatment with LUM/IVA, but that the symptoms faded within weeks or months. Patients also cited the affordability of LUM/IVA as a significant concern.

Clinical Trials

The CDR systematic review included four double-blind, placebo-controlled, RCTs (TRAFFIC, TRANSPORT, Study 112, and Study 109) and one pivotal, single-arm, open-label trial (Study 11B). In addition, the CDR review included the following studies as supplemental information: two extension phase studies (PROGRESS and Study 110) and a single-arm study conducted in patients with severe lung disease (Study 106). The study populations consisted of patients who were either six years to 11 years of age (studies 109, 110, and 11B) or patients who were at least 12 years of age (TRAFFIC, TRANSPORT, PROGRESS, Study 106, and Study 112). All of the studies included a screening phase (up to 28 days), an investigational treatment period (24 weeks), and a safety follow-up phase (approximately four weeks). The use of a placebo as the comparator in the RCTs is appropriate as LUM/IVA is currently the only treatment approved in Canada for use in the treatment of CF in patients with F508del-CFTR mutations. All of the studies compared the addition of LUM/IVA (or placebo) to ongoing standard CF-management therapies, which is reflective of how LUM/IVA would be administered in routine clinical practice.

Outcomes

Outcomes were defined a priori in the systematic review protocol. Of these, the committee discussed the following:

- **ppFEV₁** — calculated using the ratio of forced expiratory volume in one second (FEV₁) to the predicted FEV₁. Changes in ppFEV₁ were evaluated as follows:
  - Absolute change in ppFEV₁: Calculated as post-baseline value minus baseline value.
  - Relative change in ppFEV₁: Calculated and expressed in percentages as 100 × (post-baseline value – baseline value)/baseline value.
  - Proportion of patients with an improvement of ≥ 3%, ≥ 5%, and ≥ 10% in average absolute change from baseline in ppFEV₁ at week 16 and week 24.
  - Proportion of patients with an improvement of ≥ 5% and ≥ 10% in average relative change from baseline in ppFEV₁ at week 16 and week 24.

At the time of this review, there is no established MCID for absolute or relative changes in ppFEV₁ for patients with CF.
• Pulmonary exacerbations were defined as a change in antibiotic therapy for any four or more of the following signs or symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in lung function by at least 10%; or radiographic changes indicative of pulmonary infection. CDEC considered the following end points related to exacerbations:
  ▪ number of pulmonary exacerbations from baseline to week 24
  ▪ time to first pulmonary exacerbation
  ▪ incidence of having at least one pulmonary exacerbation
  ▪ pulmonary exacerbations requiring hospitalization
  ▪ time to first hospitalization for pulmonary exacerbation
  ▪ pulmonary exacerbations requiring intravenous (IV) antibiotics
  ▪ time to first IV antibiotic therapy for pulmonary exacerbation.

• Lung clearance index is a multiple breath washout test that estimates the number of lung volume turnovers required to clear the lung of an inert gas. Absolute change from baseline in LCI2.5 and lung clearance index 5% (LCI5.0) were evaluated in studies 109 and 11B, and represent the number of lung turnovers that are required to reduce the end tidal concentration of the inert gas to 2.5% and 5.0% of the starting value, respectively. Each multiple breath washout assessment was performed three times at the study visit. At the time of this review, there is no established MCID for changes in LCI2.5 for patients with CF.

• Changes from baseline in BMI, body weight, and height — these end points were adjusted for age and sex, and analyzed as BMI-for-age z score, weight-for-age z score, and height-for-age z score for patients 12 years to 20 years of age in TRAFFIC and TRANSPORT and all patients in studies 109 and 11B.

• CFQ-R is a disease-specific instrument used to evaluate changes in respiratory symptoms, digestive symptoms, emotion, and health perception. A difference of at least four points in the respiratory domain score of the CFQ-R has been cited as the MCID.

• EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) — a generic utility measure of health-related quality of life used to evaluate the current health states of patients at least 12 years of age. The MCID for the EQ-5D-3L in patients with CF is uncertain.

• Total adverse events (AE), serious adverse events (SAEs), and withdrawals due to AEs.

Absolute change from baseline in ppFEV₁ was the primary end point of TRAFFIC and TRANSPORT. Both studies also included the following five key secondary end points in a statistical testing hierarchy: average relative change from baseline in ppFEV₁ at week 16 and week 24; absolute change from baseline in BMI at week 24; absolute change from baseline in CFQ-R respiratory domain at week 24; ≥ 5% increase in average relative change from baseline in ppFEV₁ at week 16 and week 24; number of pulmonary exacerbations through week 24. Failure to demonstrate statistically significant differences stopped the statistical testing hierarchy at BMI in TRAFFIC and at CFQ-R respiratory domain in TRANSPORT.

Efficacy
Patients Aged 12 Years and Older
• Treatment with L400/IVA was associated with a statistically significant absolute increase from baseline in ppFEV₁ compared with placebo in both trials and in the pooled analysis:
  ▪ TRAFFIC: 2.60% (95% confidence interval [CI], 1.18% to 4.01%)
  ▪ TRANSPORT: 3.00% (95% CI, 1.56% to 4.44%)
  ▪ Pooled: 2.81% (95% CI, 1.80% to 3.82%).

• Treatment with L400/IVA was associated with a statistically significant improvement in relative change from baseline in ppFEV₁ in both studies:
  ▪ TRAFFIC: 4.33% (95% CI, 1.86% to 6.80%)
  ▪ TRANSPORT: 5.25% (95% CI, 2.69% to 7.81%)
  ▪ Pooled: 4.81% (95% CI, 3.03% to 6.59%).

• Results for ppFEV₁ were generally consistent across subgroup analyses based on age, ppFEV₁ at screening, and ppFEV₁ at baseline.
Across both studies, a greater proportion of L400/IVA-treated patients achieved improvements in ppFEV1 of at least 3%, 5%, or 10% based on absolute changes from baseline; and improvements of 5% and 10% based on relative changes from baseline. Fewer than half of L400/IVA-treated patients demonstrated an absolute improvement of greater than or equal to 3% in ppFEV1 (37.9% and 42.2% in TRAFFIC and TRANSPORT, respectively), fewer than one-third achieved an absolute increase greater than or equal to 5% in ppFEV1 (23.6% and 29.9% in TRAFFIC and TRANSPORT, respectively), and only a small minority achieved an increase of greater than or equal to 10% (12.1% and 13.4% in TRAFFIC and TRANSPORT, respectively). The odds ratios for achieving absolute increases in ppFEV1 of at least 3%, 5%, and 10% were:

- greater than or equal to 3% improvement: 2.20 (95% CI, 1.39 to 3.50) in TRAFFIC; 2.58 (95% CI, 1.64 to 4.04) in TRANSPORT; 2.39 (95% CI, 1.73 to 3.30) in the pooled analysis
- greater than or equal to 5% improvement: 1.73 (95% CI, 1.02 to 2.94) in TRAFFIC; 2.93 (95% CI, 1.72 to 5.00) in TRANSPORT; and 2.26 (95% CI, 1.55 to 3.29) in the pooled analysis
- greater than or equal to 10% improvement: 2.72 (95% CI, 1.20 to 6.13) in TRAFFIC; 2.46 (95% CI, 1.18 to 5.15) in TRANSPORT; 2.58 (95% CI, 1.49 to 4.45) in the pooled analysis.

In both TRAFFIC and TRANSPORT, treatment with L400/IVA was associated with a lower rate of pulmonary exacerbations compared with placebo. Similarly, treatment with L400/IVA was associated with lower rates of the following: pulmonary exacerbations requiring hospitalization and pulmonary exacerbations requiring IV antibiotic therapy. For all end points related to pulmonary exacerbations, the results demonstrated numerical or statistically significant differences in favour of L400/IVA. Rate ratios for pulmonary exacerbation end points were:

- any pulmonary exacerbation: 0.66 (95% CI, 0.47 to 0.93) in TRAFFIC; 0.57 (95% CI, 0.42 to 0.76) in TRANSPORT; and 0.61 (95% CI, 0.49 to 0.76) in the pooled analysis
- pulmonary exacerbations requiring hospitalization: 0.38 (95% CI, 0.22 to 0.67) in TRAFFIC; 0.39 (95% CI, 0.24 to 0.64) in TRANSPORT; and 0.39 (95% CI, 0.26 to 0.56) in the pooled analysis.

Pulmonary exacerbations requiring IV antibiotics: 0.36 (95% CI, 0.24 to 0.54) in TRANSPORT; 0.44 (95% CI, 0.32 to 0.59) in the pooled analysis; and could not be calculated in TRAFFIC.

Hazard ratios for pulmonary exacerbation end points demonstrated favourable outcomes for L400/IVA compared with placebo (95% CI was not reported):

- time to first pulmonary exacerbation: 0.691 and 0.533 in TRANSPORT
- time to first hospitalization for pulmonary exacerbation: 0.401 in TRAFFIC and 0.368 in TRANSPORT
- time to first pulmonary exacerbations requiring IV antibiotic therapy: 0.504 in TRAFFIC and 0.335 in TRANSPORT.

In TRANSPORT, treatment with L400/IVA was associated with statistically significant improvements in BMI (0.36 kg/m²; 95% CI, 0.17 to 0.54) and BMI z score (0.222; 95% CI, 0.096 to 0.347) compared with placebo. In contrast, L400/IVA failed to demonstrate a statistically significant difference for these end points versus placebo in TRAFFIC (BMI: 0.13 kg/m²; 95% CI, −0.7 to 0.32; BMI z score: 0.078; 95% CI, −0.062 to 0.218). The difference between L400/IVA and placebo in the pooled analysis was 0.24 kg/m² (95% CI, 0.11 to 0.37).

Neither study demonstrated a statistically significant difference for L400/IVA compared with placebo for changes in height or height z score after 24 weeks of treatment.

Results for change from baseline in body weight were inconsistent across the TRAFFIC and TRANSPORT studies. In TRANSPORT, treatment with L400/IVA was associated with statistically significant improvements in body weight (0.95 kg; 95% CI, 0.43 to 1.46) and body weight z score (0.146; 95% CI, 0.039 to 0.254). In contrast, L400/IVA failed to demonstrate a statistically significant difference for these end points in TRAFFIC. The pooled analysis difference was in favour of LUM/IVA for change from baseline in weight (0.62 kg; 95% CI, 0.24 to 1.00) and body weight z score (0.092; 95% CI, 0.014 to 0.169).

The initial CADTH review of L400/IVA considered the 24-week data from the first interim analysis of the PROGRESS extension study, which suggested that patients treated with L400/IVA maintained the effects that were observed in the double-blind phases of TRAFFIC and TRANSPORT (absolute improvement of 2.5% from baseline; P < 0.0001). Since the initial CADTH review, the manufacturer has provided additional long-term follow-up data for L400/IVA (i.e., final 96-week data from PROGRESS). The absolute improvement in ppFEV1 was gradually reduced throughout the PROGRESS study, from 2.7% (95% CI, 1.8 to 3.6) at 24 weeks, to 1.4% (95% CI, 0.5 to 2.4) at 48 weeks, and 0.5% (95% CI, −0.4 to 1.5) at 72 weeks.

Study 112 was a small study that was not designed or powered to detect differences in the end points of interest for CADTH’s review. There was no statistically significant difference between L400/IVA and placebo in Study 112 for absolute change from baseline in ppFEV1 (3.4% [95% CI, −1.2 to 8.1]), relative change from baseline in ppFEV1 (3.5% [95% CI, −3.4 to 10.4]), absolute change from baseline in BMI (0.2 [95% CI, −0.3 to 0.6]), or absolute change from baseline in CFQ-R respiratory domain (5.0 [95% CI, −2.6 to 12.7]).
Patients Aged Six Years to 11 Years

- Treatment with L200/IVA was associated with a statistically significant improvement in LCI2.5 (the primary end point) compared with placebo (least squares mean difference [LSMD]: −1.09 [95% CI, −1.43 to −0.75]) and in LCI5.0 (LSMD: −0.54 [95% CI, −0.72 to −0.35]) in Study 109.

- Treatment with L200/IVA resulted in improvements compared with placebo for absolute change in ppFEV1 (LSMD: 2.4% [95% CI, 0.4 to 4.4]) and relative change in ppFEV1 (LSMD: 3.2% [95% CI, 0.6 to 5.7]) in Study 109. In Study 11B, there was no statistically significant improvement with L200/IVA for absolute change in ppFEV1 (LSMD: 2.5% [95% CI, −0.2 to 5.2]) or relative change in ppFEV1 (LSMD: 1.5% [95% CI, −1.3 to 4.9]).

- There was no statistically significant difference between the L200/IVA and placebo groups in the rate of pulmonary exacerbations in Study 109 (rate ratio: 1.33 [95% CI, 0.70 to 2.53]). There were no statistical comparisons conducted for time to first pulmonary exacerbation, hospitalization for pulmonary exacerbation, and pulmonary exacerbations requiring IV antibiotic therapy in Study 109.

- Change from baseline in BMI was a key secondary end point of Study 109 and there were no statistically significant differences between L200/IVA and placebo for absolute change from baseline BMI (LSMD: 0.11 [95% CI, −0.08 to 0.31]) and BMI-for-age z score (LSMD: 0.03 [95% CI, −0.07 to 0.13]).

- There were no statistically significant differences between L200/IVA and placebo for changes from baseline in body weight (LSMD: 0.3 [95% CI, −0.1 to 0.7]), weight-for-age z score (LSMD: 0.04 [95% CI, −0.03 to 0.10]), height (LSMD: 0.3 [95% CI, 0.0 to 0.6]), and height-for-age z score (LSMD: 0.03 [95% CI, −0.01 to 0.08]).

- There was no statistically significant difference between L200/IVA and placebo for change from baseline to week 24 in the CFQ-R respiratory domain for either the patient or parent/caregiver versions (LSMD: 2.5 [95% CI, −0.1 to 5.1] and 2.6 [95% CI, −1.4 to 6.5], respectively).

Harms (Safety and Tolerability)

Patients Aged 12 Years and Older

- The overall proportion of patients who experienced at least one AE was similar between the placebo-treated patients (95.9%) and the L400/IVA-treated patients (95.1%). AEs that were reported in 5% or more of patients in the L400/IVA group and occurred at higher frequency compared with the placebo group were dyspnea (13% versus 8%), abnormal respiration (9% versus 6%), rhinorrhea (6% versus 4%), nasopharyngitis (13% versus 11%), upper respiratory tract infection (10% versus 5%), influenza (5% versus 2%), nausea (13% versus 8%), diarrhea (12% versus 8%), flatulence (7% versus 3%), fatigue (9% versus 8%), increased blood creatine phosphokinase (7% versus 5%), and rash (7% versus 2%).

- The proportion of patients who experienced at least one SAE was lower in the L400/IVA group compared with the placebo group (17.3% versus 28.6%, respectively). The most commonly reported SAE in any treatment group was infective pulmonary exacerbation of CF. Consistent with the efficacy data, there were more pulmonary exacerbations in the placebo group than in the L400/IVA group (24.1% versus 11.1%, respectively).

- Withdrawals due to AEs were more frequent in the L400/IVA group compared with the placebo group (4.6% versus 1.6%, respectively). An increase in blood creatine phosphokinase resulted in the discontinuation of four patients in the L400/IVA group compared with none in the placebo groups. Hemoptysis was the most commonly reported AE that resulted in patients discontinuing treatment (two patients in the placebo group and three patients in the L400/IVA group).

- The proportions of patients who experienced at least one hepatic AE were similar in the L400/IVA group (6.0%) and the placebo group (5.4%). Elevated transaminases were reported in a slightly greater proportion of L400/IVA-treated patients compared with placebo-treated patients (5.4% versus 4.6%, respectively); however, this represented a difference of only three patients. Serious liver-related AEs were reported for three patients in the L400/IVA group and none in the placebo group.

- A greater proportion of L400/IVA-treated patients (25.7%) had at least one respiratory AE compared with those who were treated with placebo (17.0%). This difference was primarily attributable to the greater proportion of L400/IVA-treated patients (22.0%) who experienced AEs related to respiratory symptoms compared with placebo (13.8%). The majority of L400/IVA-treated patients who experienced at least one AE related to respiratory symptoms (80.2%) experienced the event during the first week of treatment.
Patients Aged 6 Years to 11 Years

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

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

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

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

Patients Aged 12 Years and Older (Severe Lung Disease)

Study 106 was a prospective, open-label, uncontrolled clinical trial in patients (N = 46) who were 12 years of age or older with CF homozygous for F508del-CFTR mutation and with advanced lung disease (defined as ppFEV1 < 40%). Patients were treated with L400/IVA for up to 24 weeks.

- At week 24, the mean change from baseline in ppFEV1 was –0.4 (95% CI, –1.9 to 1.1) and three patients (7%) had an absolute increase in ppFEV1 of at least 5%.

- Over 24 weeks, there was no statistically significant changes in CFQ-R respiratory domain (LS mean change: 2.5 [95% CI, –1.0 to 5.9]) or BMI over 24 weeks (LS mean change: 0.3 kg/m2 [standard deviation (SD): 1.0]).

- The mean normalized total duration of IV antibiotics for sinopulmonary signs and symptoms was 11.4 days (SD: 18.2) during the 24-week study period compared with 19.9 days (SD: 25.9) in the 24 weeks before the study.

- During the 24-week study period, 16 patients (35%) were hospitalized (for a total of 23 hospitalizations), for an annual event rate of 1.14 (95% CI, 0.70 to 1.84) that was lower than the annual hospitalization rate in the 24 weeks before the study (2.87 [95% CI, 1.74 to 4.74]).

Matched-Registry Cohort Analysis

With respect to evaluating the impact of LUM/IVA on the rate of lung function decline in patients with CF, the manufacturer has conducted a post-hoc, matched-registry cohort analysis. This matched-registry cohort analysis compared patients with CF treated with L400/IVA from PROGRESS (N = 455) with patients from the United States Cystic Fibrosis Foundation Patient Registry (N = 1,588). The analysis suggested that the slope of decline in lung function (i.e., ppFEV1) was reduced in patients who were treated with L400/IVA compared with a matched cohort of patients from the US registry (–1.33% versus –2.29% per year over a two-year period). CADTH identified a number of important limitations with the cohort analysis that limit the ability to draw conclusions regarding the impact of L400/IVA on the long-term lung function of Canadian patients with CF. The following key issues with the study may have biased the results in favour of L400/IVA: use of registry patients exclusively from the US as it has been documented that outcomes for patients with CF in the US are worse than Canadian patients with CF; the generation of propensity scores did not include important potential confounders (e.g., pulmonary exacerbation frequency and socioeconomic status); the balance across the full range of patients and important subgroups were not presented, thus whether balance was fully achieved and how this may have affected the study results is uncertain.
Cost and Cost-Effectiveness

At the current marketed price of $170.54 per tablet, the daily cost of treatment per patient with LUM/IVA is $682, or $248,982 annually.

The manufacturer submitted a cost-utility analysis to assess the cost-effectiveness of LUM/IVA + standard of care (SoC) compared with SoC alone in patients with CF who are six years of age or older and homozygous for the F508del-CFTR mutation. SoC comprised nutritional support, airway clearance, and treatment of clinical manifestations such as lung infections. The analysis is based on an individual patient simulation model estimating long-term health care costs and quality-adjusted life-years (QALYs) over a lifetime horizon (119 years) from the perspective of the Canadian public health care payer. Clinical efficacy estimates (based primarily on ppFEV₁) were obtained from Study 109, the TRAFFIC and TRANSPORT clinical trials, and the PROGRESS extension study. In the manufacturer's base case, it was reported that LUM/IVA + SoC was associated with greater QALYs and higher costs than SoC alone, with an estimated incremental cost per QALY gained of $446,529.

CADTH identified a number of limitations with the manufacturer’s submitted economic model:

- The model lacked transparency, which led to difficulties in assessing the validity of the coding within the model, with particular difficulties in assessing the methods used within the adopted micro-simulation technique. The complexity of the model ultimately led to the necessary probabilistic analysis being too unwieldy to run.
- The probabilistic analysis did not meet requisite standards as there were inappropriate assumptions relating to the specification of certain probability distributions and not all uncertain parameters were made probabilistic.
- No stratification by age was presented (i.e., results were presented with all patients aged six and over considered as a single group). The manufacturer’s submission from 2015 was for those aged 12 and over and no new data with respect to the relative efficacy of LUM/IVA compared with SoC were supplied for this subgroup. CADTH economic guidelines specifically indicate that when input parameters vary by characteristics of patients that are likely to impact results, the analysis should be stratified by these characteristics.
- The manufacturer assumed that over time the differences in ppFEV₁ between LUM/IVA + SoC and SoC would increase. This assumption is not supported by the comparative clinical trial data given that within the clinical trials in both age groups, results suggested that the benefit from ppFEV₁ changes occurs in the initial eight weeks of treatment with curves relating to ppFEV₁ staying parallel after this period. This suggests a continuance of benefit but not an extension of benefit.
- The manufacturer assumed that after 12 years within the model, the cost of LUM/IVA + SoC would be reduced by 82% due to a generic equivalent becoming available. In addition, the manufacturer assumed patient compliance with LUM/IVA would be 96.46% each year and thus reduced drug costs accordingly.
- Finally, in addition to assuming a relationship to a reduction in exacerbations through improvements in ppFEV₁, the manufacturer incorporated an additional assumption of a further 55% reduction in exacerbations with LUM/IVA + SoC after age 12. This is unlikely to be justified and could potentially lead to double counting the potential benefit from LUM/IVA + SoC. In addition, the results of the Study 109 pediatric efficacy trial found a higher rate of exacerbations on LUM/IVA + SoC, yet the manufacturer modelled a reduction in exacerbation rates in this group.

CDR addressed the issues pertaining to treatment costs, exacerbation effects, and ppFEV₁ effects in reanalyses. The incremental cost-utility ratio (ICUR) for LUM/IVA + SoC versus SoC alone in patients aged 12 and over is $3.8 million per QALY and $7.3 million per QALY for patients aged six years to 11 years. A 98.5% price reduction for LUM/IVA is required for the ICUR in both populations to be less than $50,000, or 97% for an ICUR of $100,000.

Request for Clarification:

The drug plans that participate in the CDR process filed a request for clarification during the embargo period for the CDEC recommendation of LUM/IVA for the treatment of CF in patients six years and older who are homozygous for the F508del mutation in the CFTR gene. The questions posed by the drug plans and responses from CDEC are summarized below.
The embargoed recommendation notes that 73% of patients treated with Orkambi failed to achieve an absolute improvement of at least 5% in ppFEV1. The CADTH clinical review report notes that an accepted minimal clinically important difference (MCID) for absolute change from baseline in ppFEV1 has not been established and notes differing opinions from regulatory authorities and clinical specialists. Could CDEC comment on how the committee arrived at the threshold of a 5% absolute reduction? If applicable, could the committee also comment on the relevance of any responder analyses that could have been conducted using this threshold?

CDEC Response

CADTH’s clinical review report notes that there are differing opinions regarding the MCID for ppFEV1 in CF patients. In the absence of a formal study to determine the MCID for ppFEV1 in CF patients, CDEC’s interpretation of this end point was based on the clinical studies for LUM/IVA, the literature regarding ppFEV1 that was summarized by CADTH, and the opinion of Canadian clinical experts with experience in the diagnosis and management of patients with CF. The following was noted by the committee:

- The sample size calculations used in the TRAFFIC and TRANSPORT studies were based in part on an absolute difference in ppFEV1 of 5%, which suggests that the investigators and manufacturer thought that such a change represented a clinically important difference when designing the studies.
- The clinical experts consulted by CADTH and CDEC noted that CF specialists would generally consider an absolute improvement in ppFEV1 of at least 5% to be clinically relevant; a threshold that was also cited by the clinical expert consulted by the National Institute for Health and Care Excellence (NICE) Evidence Review Group in the UK.
- Health Canada reviewers noted that a clinically relevant outcome for patients with CF could include stabilization of lung function, an improvement in the rate of decline of lung function, or a marginal improvement in lung function, but did not note a specific threshold.

Overall, the absence of a validated MCID for ppFEV1 in CF remains a concern for the committee and makes it challenging to interpret the results of the clinical studies for LUM/IVA given that this pulmonary function measure was used as the primary end point in the trials conducted in patients who were at least 12 years of age (i.e., the TRAFFIC and TRANSPORT trials).

The manufacturer conducted a number of responder analyses based on a ≥ 3%, ≥ 5% and ≥ 10% absolute change from baseline in ppFEV1 in both the TRAFFIC and TRANSPORT studies. CDEC carefully considered the results of the analyses based on three factors: the ability of the committee to draw inferences regarding the efficacy of LUM/IVA from these analyses; the magnitude of the observed responses; and the extent to which these improvements in ppFEV1, a surrogate end point, would translate into improvements in clinical outcomes for Canadian CF patients. The committee noted the following:

- Although a greater proportion of patients achieved absolute improvements in ppFEV1 of ≥ 3%, ≥ 5% and ≥ 10%, these analyses were not primary or key secondary end points of the studies and were analyzed outside of the statistical testing hierarchy. Failure to conduct adjustment for multiplicity means that the responder analyses are inconclusive due to the inflated risk of a type I error (i.e., there was no control over the chance of a false-positive finding). This uncertainty limited the committee’s ability to evaluate the efficacy of LUM/IVA based on the responder analyses.

Based on the factors noted above, CDEC concluded that there is considerable uncertainty regarding the clinical relevance of the results for the responder analyses. Overall, these analyses were insufficient to support a reimbursement recommendation for LUM/IVA.

The embargoed recommendation notes that there is uncertainty regarding the clinical significance of the lower rate of pulmonary exacerbations reported in the TRAFFIC and TRANSPORT studies. Could CDEC provide clarity on the potential clinical relevance of the results for the other measures of pulmonary exacerbations, including those that required treatment with intravenous antibiotics (IV) and/or hospitalization? In addition, could the committee please comment on how the potential impact of a reduction in these events on the Canadian health system was considered in their deliberation and recommendation?
CDEC Response

CDEC noted that the treatment effect sizes reported for reducing pulmonary exacerbations requiring hospitalization through 24 weeks (rate ratio: 0.39 [95% CI, 0.26 to 0.56]) and requiring IV antibiotics (rate ratio: 95% CI, 0.44 [95% CI, 0.32 to 0.59]) could be clinically relevant. However, these analyses were conducted outside of the statistical testing hierarchy; they were not key primary or secondary end points when the studies were designed. Similar to the ppFEV₁ responder analyses, failure to conduct adjustment for multiplicity means that the results for pulmonary exacerbations requiring IV antibiotics or hospitalization are inconclusive due to the inflated risk of a type I error (i.e., there was no control over the chance of a false-positive finding). Moreover, 24 weeks is likely too short of a study duration to assess exacerbations as an outcome; longer-term trial designs (ideally at least one year) are required. This uncertainty compromised the committee’s ability to evaluate the efficacy of LUM/IVA based on these analyses and it was concluded that these outcomes do not provide a sufficient evidentiary base to support a reimbursement recommendation for LUM/IVA.

CDEC noted that the potential impact of a reduction in pulmonary exacerbations requiring IV antibiotics or hospitalization on the Canadian health system was incorporated into the manufacturer’s economic submission to CADTH. This is reflected in the cost-effectiveness estimates reported by CADTH and were considered in CDEC’s deliberations.

Could CDEC comment on the likelihood that improvements in exacerbations being seen in both the TRAFFIC and TRANSPORT studies were not caused by the treatment effect of Orkambi? Also, could CDEC clarify if the limitations of the studies (e.g., short duration of trials, lack of independent adjudication) would be expected to bias the results? If so, in what way would this bias the results?

CDEC Response

Regarding whether or not the reductions in pulmonary exacerbations reported in the TRAFFIC and TRANSPORT studies could be attributable to treatment with LUM/IVA requires consideration of the statistical methods used in the analysis (e.g., could it be explained by chance alone) and the internal validity of the study results (e.g., could the results be attributable to bias in the study). CDEC considered the following information:

- As noted in CDEC’s reasons for recommendation, failure of the manufacturer’s pre-defined statistical testing hierarchy prevents CDEC from concluding that these results were not due to chance alone.
- The clinical experts consulted by CADTH noted that the results are likely attributable to treatment with LUM/IVA. Limitations with the analyses include the statistical issues that were previously noted, the absence of an independent adjudication committee to confirm the events, and the short-term nature of the controlled portion of the TRAFFIC and TRANSPORT studies. It was noted that pulmonary exacerbation studies should be at least one year in duration in order to account for seasonal variation in the frequency of events.
- There were some imbalances between the treatment groups with respect to prior and concomitant usage of inhaled antibiotics and dornase alfa. CDEC noted that it is unlikely that such imbalances alone could explain the overall reduction in pulmonary exacerbations observed; however, it is possible that these imbalances had an impact on the magnitude of the effect size; that is, make the real magnitude of any observed effect uncertain. Moreover, given the nature of these imbalances, it is impossible to know if they biased the treatment effect in favour or against treatment with LUM/IVA (i.e., could the additional usage of these drugs have a protective effect or be a marker for treatment of a more severe CF disease state).

CDEC (and CADTH) noted that the magnitude of any potential bias (such as that from imbalances in baseline patient characteristics) on the estimated treatment effect of LUM/IVA for pulmonary exacerbations could not be calculated.
The embargoed CDEC recommendation stated that in a matched-registry cohort analysis that the slope of decline in lung function was reduced in patients treated with LUM/IVA by −1.33% versus −2.29%. Could CDEC clarify if this difference in the rate of the decline would be considered clinically meaningful? CDEC also noted concerns with the generalizability of this finding; could CDEC further elaborate on the implications this has for Canadian patients?

CDEC Response

CDEC carefully considered the results of the matched cohort study reported by the manufacturer and discussed the findings with Canadian clinical experts in CF. Overall, this study is not sufficient to conclude the LUM/IVA has a clinically relevant impact on the slope of decline in lung function. There are significant limitations to an analysis of registry patients matched to patients in a randomized controlled trial. As noted in CADTH’s report and by the clinical experts, there were many important issues with this analysis that limit the ability of CDEC to use this information for the purposes of making reimbursement recommendations in the Canadian context. The following key issues with the study may have biased the results in favour of L400/IVA: use of registry patients exclusively from the US as it has been documented that outcomes for CF patients in the US are worse than Canadian CF patients; the generation of propensity scores did not include important potential confounders (e.g., pulmonary exacerbation frequency and socioeconomic status); the balance across the full range of patients and important subgroups were not presented, thus whether balance was fully achieved and how this may have affected the study results is uncertain. Trial patients were selected based on enrolment in the PROGRESS open-label extension study, which excluded patients intolerant or non-adherent to LUM/IVA, and therefore may represent patients more likely to show positive treatment effects. Approximately 19% of all patients dosed in TRAFFIC or TRANSPORT were not included in the matched analysis. How these patients relate to those included in the analysis in terms of characteristics and outcomes is unknown and exclusion of these patients may introduce bias into the study, particularly given 7% were excluded for reasons related to pulmonary data during follow-up.

CDEC also noted that the authors of this study stated the following in the publication:

> Although the slowed rate of lung function decline is probably related to treatment with lumacaftor/ivacaftor, causality cannot be definitively established in the context of this analysis. Patients who participate in clinical trials might differ systematically from those who do not, although clinical trial participation is higher in patients with cystic fibrosis than those with many other disease states. Furthermore, 21% of the registry patients in the matched control group were enrolled in at least one clinical trial in 2013 or 2014. A propensity score approach was used to balance covariates associated with the rate of lung function decline between groups; however, the ability to match patients on risk factors of lung function decline is limited to the variables collected in both the registry and the clinical study. Furthermore, the registry included data from patients in the USA, whereas the PROGRESS study enrolled patients not only in the USA but also in Canada, Europe, and Australia, where the cystic fibrosis population might differ. With respect to our statistical model, estimation of average annual rate of decline was based on FEV1 measurements spanning different lengths of observation for different patients. The model also assumed that the rate of decline in FEV1 was constant over the observation period for each patient.

In summary, these limitations, related to the observational nature of the analysis and mixing of two distinct cohorts, mean that this evidence is not strong enough to support causal inferences and decision-making, especially when considered in the context of the main study findings. Furthermore, any estimates of the magnitude of the effect for Canadian patients will be limited by the inclusion of only US patients in the matched cohort registry, as there are a number of differences between the US and Canada with regards to the management of CF and US patients have been reported to have a poorer prognosis compared with those in Canada.

The embargoed CDEC recommendation states that the clinical relevance of the results for several end points were uncertain (e.g., BMI and LCI2.5). Could CDEC provide clarity regarding the nature of this uncertainty? For example, is the uncertainty related to the magnitude of the effect observed, the characteristics of the study design (e.g., duration of follow-up), or the selection of the end point?
CDEC Response
The uncertainty with the results for BMI is attributable to three important considerations: failure to consistently demonstrate improvements across the studies; the small magnitude of the observed change; and the short-term duration of follow-up. CDEC noted the following for these issues:

1. As noted in CADTH’s clinical review report, there was inconsistency in the results for changes in BMI, with statistical significance being demonstrated in only one of the trials (TRANSPORT).
2. Although the pre-planned pooled analysis suggested that treatment with LUM/IVA was associated with improvements in BMI, the magnitude of improvement was of uncertain clinical significance. Given patients in TRAFFIC and TRANSPORT were at least 12 years of age, a change in BMI at 24 weeks from baseline of less than one pound/m² is of uncertain clinical significance.
3. Canadian clinical experts consulted by CADTH and CDEC noted that longer-term trials are required to demonstrate if treatment with LUM/IVA would result in clinically meaningful improvements in BMI for Canadian patients compared with current clinical practice.

As noted in CADTH’s clinical review report, there is no established MCID for LCI2.5 and this end point is not used in Canadian clinical practice. Hence, it is not possible to conclude whether or not the results are clinically relevant, particularly in patients who have relatively normal lung function.

Could CDEC provide commentary regarding the type of clinical outcomes that would be required to address the uncertainty in the study results that was noted in the embargoed recommendation document (e.g., in a list of research gaps that could be addressed through future studies including real-world effectiveness data)?

CDEC Response
Data regarding the following end points would be beneficial in order to accurately assess the clinical benefit of LUM/IVA:

- Controlled studies evaluating adjudicated pulmonary exacerbations over at least one year of treatment.
- Controlled studies in patients with rapidly progressive disease, in those who experience a greater number of pulmonary exacerbations, in patients with severely impaired pulmonary function (FEV1 < 40%).
- Controlled studies evaluating slope of decline in lung function.
- Long-term end points such as time to lung transplantation and survival.

CDEC noted that some of these outcomes could be addressed through the collection of real-world effectiveness data in order to account for the long duration of follow-up and low event rates.

Could CDEC clarify what information would be required to develop clinical criteria that would facilitate the identification of patients who are at risk for rapid deterioration (i.e., the subgroup of patients identified by clinical specialists in whom there may be a place in therapy for LUM/IVA)?

CDEC Response
As noted in CADTH’s report and by the clinical experts, the controlled studies were limited to patients with stable disease; hence, these studies cannot be used to evaluate the effect of LUM/IVA on patients who are at risk for rapid deterioration. CDEC concluded that the available clinical and pharmacoeconomic evidence submitted by the manufacturer is insufficient to support reimbursement recommendations that include starting and/or stopping criteria for patients at risk of rapid deterioration.

For younger patients six to 11 years old, Orkambi was associated with a statistically significant improvement in lung function (based on LCI2.5) after 24 weeks of treatment, but CDEC noted that the clinical relevance of this result could not be
determined because the threshold for determining clinical importance of the results for the test that was used has not been established. Can CDEC clarify what information would be required to determine the clinical significance of this result?

CDEC Response

As noted in CADTH’s report and by the clinical experts, there is no established MCID for the LCI2.5 and this end point is not used in Canadian clinical practice. CDEC noted that the following information would be necessary to determine whether LCI2.5 is a clinically meaningful end point:

- Demonstration that LCI2.5 is a valid surrogate end point. Specifically, such studies should show that there is a strong, independent, consistent association between LCI2.5 and clinical end points in CF patients. Also, that there is evidence that improvement in LCI2.5 has consistently led to improvement in clinical end points.
- Establishment of the magnitude of improvement in LCI2.5 that is associated with improvement in clinical end points (i.e., the MCID).
- Standardized methods for LCI2.5 measurement and analysis.

Could CDEC please comment on whether or not the committee feels that the pivotal studies included in CADTH’s review were well-designed and well-conducted?

CDEC Response

CDEC concurs with CADTH and the clinical experts, in that the clinical studies submitted by the manufacturer were generally well-designed and well-conducted. However, CDEC has noted that the clinical studies must be interpreted in accordance with the statistical testing hierarchy that was pre-planned by the manufacturer. CDEC does not agree with the manufacturer’s decision to calculate and report $P$ values for secondary end points after failure of the statistical testing hierarchy.

CDEC also noted that the design of the clinical trials left some important gaps in the evidence that should be addressed through further studies. These are documented above, in CDEC’s response to question six from the jurisdictions.

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

July 18, 2018 Meeting (Initial):

Regrets:

None

Conflicts of Interest:

None

September 19, 2018 Meeting (Request for Clarification)

Regrets:

None

Conflicts of Interest:

None
References