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Effect of CFTR Modulators on Respiratory Function in Adults with Cystic Fibrosis

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Abstract

Cystic Fibrosis (CF) is an autosomal recessive disorder that shortens one's life due to its effect on the cystic fibrosis transmembrane regulator (CFTR) gene. CFTR modulator medications can correct the CFTR gene and consist of a potentiator (ivacaftor), and corrector (lumacaftor, tezacaftor and elexacaftor). This research and literature review sought to evaluate if lung function improved in an individual with genetically confirmed CF after being started on CFTR modulator medications. To complete the review, six databases were searched which included: CINAHL, PubMed, Clinical Key, Cochrane Library, Embase and Dynamed Plus. Both keyword and mesh terms were used to define a set of the literature discussing CF and CFTR modulator use. A total of 24 studies were included and met the inclusion criteria of: peer reviewed, published within the past six years, had more than 20 study participants, and were not limited case reports. Phase 2 studies were included for triple therapy with elexacaftor-tezacaftor-ivacaftor and duo therapy with tezacaftor-ivacaftor, due to limited research in this area. The research indicated that individuals with G551D, non-G551D gating mutations, Gly-Asp-CFTR and ARG117HIS mutations, had an overall improvement in ppFEV1 after initiation of ivacaftor. Heterozygous and homozygous Phe508del, had the largest improvement in ppFEV1 with elexacaftor-tezacaftor-ivacaftor. Ivacaftor and lumacaftor-ivacaftor appear to have age dependent changes on ppFEV1. Individuals with severe lung disease appear to have a positive response to treatment, although it may be delayed.

Keywords: Cystic Fibrosis, drug therapy, Cystic Fibrosis Transmembrane Conductance Regulators, membrane transport proteins, membrane proteins, CFTR modulator.

Effect of CFTR Modulators on Respiratory Function in Adults with Cystic Fibrosis

Introduction

Cystic Fibrosis (CF) is an autosomal recessive disorder that effects the cystic fibrosis transmembrane regulator (CFTR) gene. This gene encodes the chloride channel, and this dysfunction leads to mucus hypersecretion, airway inflammation, and recurrent lung infections (McCance & Huether, 2019). Individuals can also have gastrointestinal dysfunction including pancreatitis, pancreatic insufficiency, and male infertility (DynaMed Plus, 2018). CF affects Caucasians most often and is typically diagnosed in childhood; it is among the several conditions tested with prenatal and newborn screening. DynaMed Plus (2018) states that CF is the most common life-threatening autosomal recessive disease and is diagnosed per 100,000 live births out of 2,228,138 newborns.

Individuals with CF have a shortened life span. Per the Cystic Fibrosis Foundation, in 2018 the median age at death was 31. Improved therapies for this genetic disorder have now extended the life expectancy to 44 for those born between 2014 and 2018 and 47 for those born in 2018 (CF Foundation, 2018). Most often, the cause of morbidity and mortality is pulmonary disease (DynaMed Plus, 2018; Graeber et al., 2018; Konstan et al., 2017). A class of medications that have been in development over the past decade are CFTR modulator medications, with ivacaftor being the first approved for use in 2012 (Taylor-Cousar et al., 2017). These medications aim to correct the protein mutation and improve the processing, trafficking, and opening across the epithelial cell. By doing so, respiratory function may be improved which could potentially extend one's life even further.

Statement of the Problem

Individuals with cystic fibrosis have a multi-system disorder caused by a genetic mutation in CFTR gene (Davies et al., 2018; Wainwright et al., 2015). Respiratory

complications are common and can include chronic cough and sputum production, frequent pneumonia, severe bronchitis and bronchiectasis, and colonization of a variety of respiratory pathogens (DynaMed Plus, 2018; McCance & Huether, 2019). CF is a progressive obstructive lung disease and over time, leads to respiratory failure (Konstan et al., 2017). CFTR modulators correct the CFTR mutation which may reverse the effects caused by the disease. Modulator medications are made up of a potentiator (ivacaftor), which improves chloride transport and is provided with or without a corrector (tezacaftor, lumacaftor, elexacaftor) which improves processing of the CFTR protein (Taylor-Cousar et al., 2017; Davies et al., 2018). By providing these medications to an individual with CF, the CFTR regulator improves chloride transport which thins the mucus and may improve lung function.

Research Question

If an individual with genetically confirmed CF is started on CFTR modulator medications, will lung function improve?

Literature Review

Ongoing studies are evaluating the overall effect that CFTR modulators ivacaftor, lumacaftor, tezacaftor and elexacaftor have on sweat chloride, respiratory status, BMI, exercise tolerance and bacterial colonization. The safety of the medication has been evaluated in phase 2 and phase 3 trials. For this literature review, the focus is on the effect of CFTR modulators on respiratory status by use of percent predicted FEV1 (ppFEV1).

Methods

A literature review was performed using electronic search databases: CINAHL, PubMed, Clinical Key, Cochrane Library, Embase and DynaMed Plus. Both keyword and mesh terms were used to define a set of the literature discussing CF and CFTR modulator use. The searches revealed over 400 studies; A total of 24 studies were included in this literature review.

To be included, studies needed to be peer reviewed, focus solely on CFTR modulators, did not only evaluate safety, discussed more than the history of the medication, were not limited case reports, had more than 20 study participants and were published in the past six years. The focus of this review is adults aged 18 years and older, although due to limited research in the area, studies that included subjects aged 6 and older were reviewed. When data for age groups was stratified, it is reported and discussed as to how the medication may affect different aged individuals. Phase 2 studies were included in the literature review for triple therapy with elexacaftor-tezacaftor-ivacaftor and duo therapy with tezacaftor-ivacaftor, due to limited research in this area. Otherwise, all other phase 2 studies were excluded due to not adding more breadth to the literature review.

Pathophysiology of CF

CF is an autosomal recessive disorder caused by a defect of the CFTR protein on chromosome 7 which leads to reduced epithelial chloride ion transport and increased sodium absorption (McCance & Heuther, 2019). The CF transmembrane conductase regulator (CFRCR) protein is located on the surface of epithelial cells throughout the airways, bile ducts, pancreas, sweat glands, paranasal sinuses, and vas deferens (McCance & Heuther, 2019). In the lungs, the CFTR defect leads to viscous mucus that collects bacteria and neutrophils that can lead to remodeling of the airway and bronchiectasis (McCance & Heuther, 2019). Respiratory failure occurs slowly over time and is the most common cause of death in individuals with CF (Graeber et al., 2018; McCance & Heuther, 2019). Treatments in CF are started early in life and focus on pulmonary health to thin and clear the mucus from the lungs to reduce infection, and inflammation risks (McCance & Heuther, 2019).

There are over 2000 mutations which are divided into six classes depending on severity of disease with class I through III having more severe disease than classes IV, V and VI (Heijerman et al., 2019; Jennings et al., 2017; McCance & Heuther, 2019; Rowe et al., 2014; Taylor-Coussar et al., 2017; Veit et al., 2016). The mutations studied most with CFTR modulator therapy are: Gly551Asp-CFTR, Arg117His-CFTR and Phe508del. Gly551Asp-CFTR mutation is also known as G551D and is found in 4% of patients worldwide (McKone et al., 2014). This is the most common class III mutation and causes defective gating which reduces channel opening of the epithelial cell (Barry et al., 2014; McKone et al., 2014; Rowe et al., 2014; Veit et al., 2016); This leads to decreased chloride transport through this channel (McKone et al., 2014; Taylor-Cousar et al., 2016). Arg117His-CFTR mutation is a class IV mutation and known as R117H. Its main defect is reduced channel gating along with impaired CFTR channel conductance (Moss, et al., 2015; Veit et al., 2016). This mutation is found in around 3% of patients with CF and has a median life expectancy of 50 years old (Moss et al., 2015). Individuals with this mutation will have variable presentation due to residual function of the CFTR protein (Moss, et al., 2015). The most common CF mutation is Phe508del, also known as F508del, and is present in 73% of individuals with CF worldwide (Coussar et al., 2017; Donaldson et al., 2018; Elborn et al., 2016; Hubert et al., 2017; Rowe et al., 2017; Taylor-Heijerman et al., 2019; Wainwright et al., 2015)). This class II mutation causes protein misfolding, and reduced CFTR proteins at the cell surface which leads to reduced processing and channel opening and minimal CFTR chloride transport (Donaldson et al., 2018; Elborn et al., 2016; Hubert et al., 2017; Taylor-Coussar et al., 2017; Wainwright et al., 2015; Veit et al., 2016). The protein dysfunction in Phe508del causes effects in the pancreas, gastrointestinal tract, reproductive tract, and respiratory system (Rowe et al., 2017).

Ivacaftor monotherapy effect on lung function

A study by Barry et al. (2014) evaluated the effect of compassionate use of ivacaftor in individuals with CF that had severe lung disease (ppFEV1 <40%), and/or listed on a transplant list, or would have adverse clinical outcomes if they had to wait for funding to receive ivacaftor. To complete this study, they used a retrospective case-control study design with subjects living in the United Kingdom and Ireland. A total of 46 subjects were enrolled in the study with the treatment group (n=21) having severe lung disease (baseline ppFEV1 26.5%) and at least one G551D allele. These subjects were matched with control subjects (n=35) who did not carry the G551D allele (baseline ppFEV1 30.3); All subjects completed the trial and were aged 20-31.

After treatment initiation, subjects had a significant improvement in ppFEV1 with a mean SD 0.91 to 1.062 (p=0.0095) and a relative increase of 16.7% when compared to the placebo. This improvement adjusted treatment subjects' baseline ppFEV1 from a mean of 26.5% (7.2) to 30.7% (9.9; p=0.0068). When compared to the control group, the group receiving ivacaftor had a greater increase in ppFEV1. The ivacaftor group had a 3.8 (0.2-7.7) absolute change compared to 0.6 (-2.1 to 2.8) of the control group with a p value of 0.009. Lung function was noted to trend upward throughout the study with the largest improvement in ppFEV1 at day 180 of 3.0 percentage points (p=0.024).

The study is limited due to it being a retrospective study with a small sample size. It also had a variable post-medication follow-up from 3 to 9 months between subjects. All these factors could increase bias and skew the data.

De Boeck et al. (2014) studied the effect that ivacaftor has on non-G551D gating mutations; the researchers aimed to evaluate if it would potentiate chloride transport in individuals who carry one of these mutations which would result in improved clinical outcomes.

This was a multi-national (United Stated, France, and Beliguim), multi-center (12 different sites) study named KONNECTION. It was completed in two parts with the first being a double blind, placebo-controlled crossover design. Each study arm lasted for 8 weeks with a 4-8-week washout period. The second phase was an open-labeled 16-week study in which all participants received the study drug. Individuals could choose to enroll in the study if they had a confirmed diagnosis of CF, were aged greater than (>) 6 years of age, had at least one non-G551D gating mutation (G178R, S549R, G551S, G970R, G1244E, S1251N, S1255P, G1349D) and a ppFEV1 of >40%. A total of 39 patients were enrolled in the study, with 36 completing the full study.

Subjects mean baseline ppFEV1 was balanced at the start of the study with the full study population having a baseline ppFEV1 of 78.4% (range 42.9 to 118.7), 77.7% (range 43.0 to 118.7) for the ivacaftor to placebo group (n=20) and 79.1% (range 42.9 to 104.1) for the placebo to ivacaftor group (n=19). Results of the first phase of the study show that ppFEV1 had a significant improvement ($p<0.0001$) when participants were provided ivacaftor for 8 weeks. The improvement in ppFEV1 occurred within the first two weeks of treatment (7.23 percentage points) and was maintained through the study (8.13 percentage points). The opposite occurred in individuals that received the placebo, their absolute change from baseline in ppFEV1 was noted to decline starting at week 2 and continued through week 8 with a total decline of at least 3.2 percentage points. Subjects that enrolled in the extension study for 24 weeks (n=18 total for ivacaftor for 24 weeks), continued to have an overall increase in ppFEV1 of 13.5 (range -6.9 to 36.5) percentage points at week 16 which was overall stable at week 24.

Study limitations include a small sample size, data between adults and pediatrics was not separated and each study arm for phase one was relatively short (8 weeks). The second phase of

the study was for 24 weeks, however only 18 subjects enrolled. These limitations could increase bias and potentially skew the data.

The effect of ivacaftor in CF patients with at least one GlyAsp-CFTR mutation was studied by Hubert et al. (2018). The goal of their study was to monitor individuals started on ivacaftor before June 1, 2013 and had received at least 1 to 2 years of treatment. To complete the study, the researchers used a multicenter, retrospective, observational design using French CF Registry data from 25 French CF Centers. Subjects (n=57) were aged 6 years or older (n=30 children/adolescents; n=27 adults), had at least one GlyAsp-CFTR allele and had received ivacaftor for at least 1 to 2 years; n=56 patients (98%) finished the first year and n=48 (84%) were still included at the end of the second year.

At the start of the study, baseline ppFEV1 was higher in children aged 6-12 (n=16) at 84.3% (range 71.6 to 97), and adolescents aged 12-18 (n=14) at 86.0% (range 61.6 to 110.4) when compared to the adults (older than 18) at 59.5% (32.3 to 86.7). The results of the study indicated that subjects aged 6-12 did not have a significant increase in ppFEV1 after receiving ivacaftor for one (n=16; ppFEV1 change 7.3 +/-19.0; p= not significant (NS)) or two (n=11; ppFEV1 change 6.1 +/-18.4; (p=NS)) years. The age group that had the largest increase in ppFEV1 were those aged 12-18 with an absolute change of 12.5 +/- 11.5 percentage points (n=14; p=0.004) at the end of the first year and 12.3 +/- 6.1 percentage points (n=14; p=0.053) at the end of the second year. Adults aged greater than 18 had a significant change in absolute ppFEV1 after the first year (n=26; ppFEV1 change 7.0 +/- 12.5; p=0.009) but not after the second year of treatment (n=22; ppFEV1 change 5.5 +/- 13.9; p=NS). When all aged subjects were combined, the absolute change of ppFEV1 was 8.4% +/- 14.3 (n=56; p=0.0001) the first year and 7.2% +/- 15.5 (n=44; p=0.006) the second year. When considering baseline FEV1,

those with FEV1 >40% had a greater improvement of ppFEV1 (n=49; year one: ppFEV1 change 9.1% +/- 15.3; p=0.0004. year two: ppFEV1 change 7.8% +/- 17.2; p=0.017) than those that had a baseline FEV1 <40% (n=7; year one: ppFEV1 change 5.0% +/- 8.8; p=0.126. year two: ppFEV1 change 4.8% +/- 6.8; p=0.069).

Clinically, this study is helpful because it provides information on age-dependent effects of treatment. It also evaluates the difference in response of treatment between those with lung function that is severe (<40%) to those with ppFEV1 >40%. Limitations of the study are that it was observational, retrospective, un-blinded and did not have a control to compare the data to during the study. This could increase bias and potentially skew the effect of treatment and reduce the ability to compare overall treatment effect.

Guimbellot et al. (2019) aimed to gain further information on ivacaftor's effect in individuals with non-G551D gating (Class III) mutations by conducting a follow-up extension study on the effectiveness of ivacaftor over a 6-month period. The study was a longitudinal, cohort design that included three different cohorts and used data from the Unites States (US) CF Foundation Patient Registry. The study included subjects (n=21) 6 years of age or older with at least one non-G551D gating mutation, the second allele could not be G551D or R117H with no prior exposure to ivacaftor. This study did not have a control and was un-blinded; All subjects enrolled received ivacaftor. At the conclusion, 18 (86%) completed the entire 180-day study of follow-up; 2 were lost to follow-up and 1 withdrew.

Baseline mean ppFEV1 of patients aged less than 18 (n=11) was 88.7% which was notably higher than the mean baseline ppFEV1 of adults (>18; n=10) at 45.2%. After treatment was initiated, there was a significant increase in mean absolute ppFEV1 at one month of 9.3 percentage points (95% CI 4.3 to 14.4; p = 0.0011) which was sustained at 3 months (8.4%; 95%

CI 1.4 to 15.3; p = 0.0214) and 6 months (10.9%; 95% CI 2.6 to 19.2; p = 0.0134). When comparing the pediatric subjects to the adult subjects, the pediatric patients had a significant change in absolute ppFEV1 at 1 month (n=11; ppFEV1 change 7.5%; 95% CI 2.0 to 13.0; p=0.0120), although at 3 (n=11; ppFEV1 change 7.2%; 95% CI -4.6 to 19.1; p=0.2039) and 6 months (n=9; ppFEV1 change 6.1%; 95% CI -4.1 to 16.2; p=0.2058) it was sustained but no longer significant. Adults (>18) were noted to have an overall improvement in absolute ppFEV1 at 1 (n=9; ppFEV1 11.5%; 95% CI 1.0 to 22.0; p=0.0350), 3 (n=9; ppFEV1 change 9.8%; 95% CI 0.8 to 18.7; p=0.0364) and 6 months (n=8; ppFEV1 change 16.4%; 95% CI 1.1 to 31.8; p=0.0393). The adults were noted to have a progressive increase in ppFEV1, unlike the pediatric patients which had a more acute, sustained improvement.

Limitations of the study were the small sample size, observational study design and not having a control or blinding. This can increase bias and potentially skew the data. Although, this study by Guimbellot et al. (2019) is helpful in age related treatment response.

Assessing the effect of ivacaftor in a real-life setting was studied by Kirwan et al. (2019) by comparing clinical characteristics and healthcare utilization before and after treatment initiation. To complete this longitudinal cohort study, subjects could enroll if they were 6 years or older, had at least one G551D mutation and had received ivacaftor for at least 36 months prior to the end of 2017 and started before January 2015. Data was collected from the CF Registry of Ireland which contains information on 11 CF centers and more than six CF clinics in Ireland. A total of n=80 patients were eligible for the longitudinal trend analysis, four patients stopped ivacaftor before 2017 and three patients died before 2017; Although, they all had 36 months' worth of data and were included in the study.

The trends for ppFEV1 were dependent on age and were found to have an age group intercept of $p < 0.01$. The subjects younger than 12 (n=27), had an average baseline ppFEV1 of 90.3% which slowly increased after ivacaftor initiation; By the end of the 3-year period, ppFEV1 increased by 2.26% (95% CI, 71 to 91.8%). Adolescent subjects (aged 12 to 18; n=18) had an average baseline ppFEV1 of 81.4%. Unlike the children, the adolescents had a significant change in ppFEV1 after initiation of the ivacaftor of 9.1% (96% CI, 4.6 to 13.6%) which was sustained during the 3 years of treatment. When compared to the patients aged >18 (n=35), mean ppFEV1 at baseline was 60.4%, there was again no significant decline in FEV1 noted in this population the 3 years prior to the start of ivacaftor (95% CI, -2.3 to 0.9%). Once ivacaftor was initiated, an increase of 7.4% (95% CI, 4.9 to 9.9%) was noted in ppFEV1. Although, unlike the patients aged less than 18, there was a downward trend in the ppFEV1 over the next 3 years (decline of 1.74%, 95% CI, -3.1 to -0.4). One of the largest factors in decline was noted to be infection with *P. aeruginosa*; Sex (95% CI, -7.8 to 7.9%), BMI (95% CI, -23.9 to 2.7%) *or S. aureus* infection (95% CI, -9.2 to 7.1%) did not have a significant effect on ppFEV1. Although, this improvement was not sustained over the 36-month trial and was noted to trend down by the end of the study period.

Limitations of the study are due to the study design in that it was not a randomized, blinded or control trial. It was observational using limited data from a CF registry which could increase bias and skew the data presented. It would be helpful to have control data to evaluate if ppFEV1 remains above pulmonary decline in aged matched controls with treatment of ivacaftor. It is also important to note that the overall decline in ppFEV1 correlated with lung infection.

A post-hoc study by Konstan et al. (2015) sought to evaluate if response to treatment with ivacaftor is consistent across an entire population. They also aimed to assist in interpreting data

from two phase 3 trials (STRIVE and ENVISION) into clinical practice. Data from STRIVE (12 years of age and older) and ENVISION (6-11 years of age) were pooled for a total of 209 subjects; 109 subjects had received ivacaftor and 100 the placebo. To be included in these studies, subjects had a confirmed diagnosis of CF and at least one G551D-mutation.

Once enrolled, subjects were assigned to tertile groups dependent on the amount of change in baseline ppFEV1 after ivacaftor treatment. Results indicate that overall, ivacaftor treatment was noted to cause a significant improvement in ppFEV1 through week 48 across all tertiles. The lowest tertile was divided between placebo (n=34, ppFEV1 < -2.65) and ivacaftor (n=37, ppFEV1 <5.56) groups. Comparing results within this tertiary group indicate an absolute change from baseline ppFEV1 of 7.97 percentage points (95% CI 6.48, 9.47; p <0.0001). When the lowest tertiary treatment group was compared to the placebo overall, there was an increase of 2.29 percentage points (95% CI 0.40, 4.19; p 0.0179) in absolute ppFEV1. The middle tertiary group was divided between the placebo (n=33, ppFEV1 between -2.26 and 1.74) and ivacaftor (n=36, FEV1 between 5.56 and 13.59) groups. Comparing results within this tertiary group indicate an absolute change in ppFEV1 of 9.66 percentage points (95% CI 8.77, 10.55; p <0.0001). When the middle tertiary treatment group was compared to the overall placebo, there was an increase of 9.66 percentage points (95% CI 7.82, 11.49; p<0.0001) in absolute ppFEV1. The upper tertiary group was divided into a placebo (n=33, FEV1 >1.74) and ivacaftor (n=36, FEV1 >13.59) groups. An overall increase in absolute ppFEV1 of 15.6 percentage points (95% CI 13.00, 18.19; p <0.0001) was noted when comparing within the upper tertiary group. When the upper tertiary treatment group was compared to the overall placebo an increase in ppFEV1 of 20.73 percentage points (95% CI 18.5, 22.96; p <0.0001) was found. Based on pooled data between the two studies, the number needed to treat (NNT) to increase ppFEV1 by five or more

percentage points was 1.90. This indicates that a small number of patients need to be treated to gain a positive treatment effect. When ppFEV1 was plotted in response curves, the treatment group was shifted to the right of the placebo group indicating that there was a treatment effect and that most patients benefit from initiation of ivacaftor. This is also true when considering overall change within tertiles of the treatment group, all tertiles had a change in ppFEV1. Combination of the response curve with overall tertile change indicate that subjects that received ivacaftor had an overall improvement in lung function.

Subjects were divided into tertiles based on the percent improvement in ppFEV1, evaluation of baseline ppFEV1 prior to the start of the study indicates that it ranged from 64 to 71%. Baseline ppFEV1 was not predictive of the total treatment effect, for example, individuals in the lower tertile receiving ivacaftor had an average ppFEV1 of 72.1% and the upper tertile had an average of 68.9%. This is not a large variance, although clinicians need to be aware that medication effects may be different in each patient treated, they cannot use baseline ppFEV1 as an indicator of potential treatment response. A limitation of the study is that Konstan et al. (2015) did not separate the data between age groups. Previous studies have indicated that treatment response may differ between age groups. It is important to understand that this could potentially skew the data due to children having higher ppFEV1 at baseline and less severe lung disease than adults aged >18.

PERSIST was an open-label, 96-week extension study completed by McKone et al. (2014) that aimed to identify if long-term use of ivacaftor was safe, well tolerated and had a sustained effect in patients with Gly551Asp-CFTR mutation. To be eligible for enrollment, subjects had to have completed the 48-week STRIVE or ENVISION studies and received a placebo or treatment with ivacaftor. Once enrolled in the PERSIST study, all subjects received

150 mg of ivacaftor every 12 hours. The researchers enrolled n=192 patients (n=144 adolescents/adults from STRIVE; n= 48 children from ENVISION) with n=173 (90%) completing the 96 weeks of treatment. At the completion of the study, a total of 144 weeks of treatment would be completed in the individuals who had received the study drug during the STRIVE or ENVISION trial and 96 weeks for those that received the placebo.

Subjects who were transitioned to receive ivacaftor from placebo in the STRIVE studies, had a significant rise in absolute ppFEV1 within the first 48 weeks of treatment (9.4%; SD 8.5) which was sustained over 96 weeks (9.5%; SD 1.2). A similar increase in ppFEV1 was noted in subjects transitioning from ENVISION placebo treatment to ivacaftor treatment in PERSIST at both 48 (8.8%; SD 12.5) and 96 weeks (10.5%; SD 10.5). Subjects who received ivacaftor in STRIVE and then were continued on the treatment through PERSIST had similar improvements in ppFEV1 at 46 (9.4%; SD 8.3), 96 (9.1%; SD 10.8) and 144 weeks (10.3%; SD 12.4). Similar results were noted with subjects transitioning from ENVISION to PERSIST with an absolute sustained increase in ppFEV1 over 48 (10.2%; SD 15.7), 96 (9.0%; SD 15.2) and 144 weeks (9.0%; SD 15.2).

Providing ivacaftor appears to have a significant, sustained improvement in ppFEV1 over 144 weeks of treatment in individuals with at least one G551D-mutation. The effect was noted to be greater in subjects from ENVISION which were children aged 6-11 as indicated by their absolute change in ppFEV1 being higher in this group than any other group. This study was limited because it could only enroll subjects that were in the ENVISION or STRIVE studies, although even with this limitation they were able to enroll a large sample size. This was a closed label design in which all study participants received the treatment, it would be helpful to have a

control group to compare the overall change in ppFEV1 over 144 weeks to understand how this may differ from an un-treated population.

KONDUCT was a 24-week, multicentered, phase 3, double blinded, placebo-controlled, parallel group trial completed by Moss et al. (2015) to assess the efficacy and safety of ivacaftor in patients with Arg117*His-CFTR* mutation. Subjects could enroll in the study if they had a confirmed diagnosis of CF, were 6 years of age or older and had a ppFEV1 >40%. All subjects had to have at least one Arg117His mutation. A total of n= 69 patients entered the trial with n=67 (97%) completing the full length. After a washout period of three to four-weeks, subjects could choose to enroll in KONTINUE, an optional extension study. Subjects that enrolled in the open-label KONTINUE trial received ivacaftor for an additional 104 weeks.

When the treatment group (n=34) was compared to the placebo (n=35), the change in absolute ppFEV1 from baseline was not significant (2.6%; 95% CI of 2.1; -1.13 to 5.35; p 0.20). When divided into age groups, those aged 6-11 that received ivacaftor (n=9; ppFEV1 -2.8%) were compared to placebo (n=8; ppFEV1 3.5%). There was a treatment difference of -6.3 (95% CI -11.96 to -0.71; p 0.03) which favored the placebo. Subjects aged greater than 18 (n=24) that received ivacaftor (ppFEV1 change 4.5%) had a significant treatment difference when compared to the placebo (n=26; ppFEV1 change -0.5%) of 5.0 percentage points (95% CI 1.15 to 8.78; p 0.01). Data for adolescents aged 12-17 was not provided due to there only being two subjects in this age group. When separated between KONDUCT and KONTINUE trials, the KONDUCT 24 week trial found that subjects aged 18 and older had a significant improvement in ppFEV1 from baseline when compared to the group that received the placebo of 5.0% (95% CI 1.15 to 8.78; p = 0.01). It also found that ppFEV1 was increased 2.6% in ivacaftor vs 0.5% in placebo (p=0.20; 95% CI -1.13 to 5.35), which was not significant. During the 3-4-week washout period,

ppFEV1 returned to baseline after the treatment was removed in subjects that had received ivacaftor during the KONDUCT study. The 12-week KONTINUE found that ppFEV1 increased 5.1 percentage points ($p < 0.0001$) after ivacaftor was initiated in both the placebo to ivacaftor and ivacaftor to ivacaftor groups. When the two groups were separated, the placebo to ivacaftor group had an increase in absolute ppFEV1 of 5.5 percentage points ($p=0.0016$) and the ivacaftor to ivacaftor had an increase in absolute ppFEV1 of 4.7 percentage points ($p=0.0036$). The extension study provided longitudinal data in that the change in ppFEV1 may be sustained over 104 weeks of treatment.

Individuals with Arg117His mutation may have a significant increase in ppFEV1 after initiation with ivacaftor over a prolonged period. It is important to understand that the Arg117His mutation is associated with more severe lung disease in adult life (Moss et al., 2015). This was most noted by the baseline ppFEV1 of 64.5% in adults when compared to children with an average of 95.8% in this study; the lower baseline ppFEV1 may correlate with the adults having a significant improvement in ppFEV1 after ivacaftor initiation. The adults (>18 years old) were also noted to have a larger treatment effect then those aged 6-11 years of age (5% versus -6.3%). The study was limited due to a small sample size; each study arm only had 30-35 subjects. A larger number of subjects in each study arm may provide greater information on the overall effect of the medication on lung function and reduce the risk of bias.

Ronan et al. (2018) note that CT imaging may be a more reliable indicator of lung function. They report that individuals with a normal ppFEV1 could have mild bronchiectasis with a CT scan and that ivacaftor has been shown to demonstrate improvement on CT scans. The goal of this study was to evaluate if CFTR modulator therapy will improve CT scans, inflammatory markers, and changes in lung microbiota. To complete this prospective study,

patients could enroll if they were aged 6 years or older, had at least one G551D mutation and a patient at the CORK CF Center. The study enrolled n=33 patients (n= 20 adults; n=13 pediatric), follow-up was not discussed. Baseline characteristics were not balanced, 70% were males, and 85% had a second mutation of Phe508del.

At the start of the study, the average baseline ppFEV1 was 75.21% (SD, 20.7). ppFEV1 had a significant trend upward over the 12-month study period with a mean increase of 10.3 percentage points ($p<0.001$). Of the participants, 18 were adults and completed the low-dose CT studies. Within this group, mean increase of ppFEV1 was 12 percentage points ($p <0.01$) and CT scans had significant reductions in total Bhalla score ($p<0.01$), peri bronchial thickening ($p = 0.035$), and extent of mucus plugging ($p<0.01$). Evaluation of bronchiectasis, number of bullae, emphysema, and presence of sacculation or abscesses did not have a significant change.

This study is helpful because it provides a potential additional mean to evaluate change in lung function with use of a CT scan. However, Ronan et al. (2018) did not correlate between lung function (ppFEV1) and change in CT scan. This would be helpful in future studies along with a control group comparison in the understanding of how this information could be more useful clinically. The study was also observational which may increase bias, skew the data, and reduce the ability to calculate statistical significance.

A longitudinal study by Rowe et al. (2014) sought to further evaluate the overall long-term effect that ivacaftor had on mucocilliary transport, intestinal pH profiles, the nature of chronic infection on pulmonary inflammation and sweat gland secretion. They also aimed to evaluate the treatment's use in a larger population, since this had not yet occurred. To complete the study, they targeted individuals with at least one G551D mutation aged 6 years of age and

older with no previous exposure to ivacaftor at multiple sites (28 centers). A total of 151 were prescribed ivacaftor and 133 (85%) continued the study through 6 months.

The results indicated that baseline ppFEV1 (82.6%) increased (90.1%) after patients received ivacaftor for 6 months (p=<0.001). The initial improvement in lung function was noted at 1-month with a mean absolute increase in ppFEV1 of 6.7 percentage points (95% CI 5.2-8.3; p <0.001) and this was sustained over 3 (mean absolute increase in ppFEV1: 5.4%; 95% CI 4.0 to 6.7; p <0.001) and 6 months (mean absolute change ppFEV1: 6.7%; 95% CI 4.9 to 8.5; p <0.001). When age groups were divided, it was noted that subjects aged 6-11 had the smallest improvement in ppFEV1 which was hypothesized to be due to less severe lung function at baseline.

This study by Rowe et al. (2014) is helpful clinically because it provides a physiologic understanding of how CFTR modulators may be assisting with improving lung function. The limitations of the study were that data was not provided for age variance; the study only stated that children aged 6-11 had less change in ppFEV1. It would be helpful to further understand the difference between groups by having the ability to evaluate the data. This was also an observational study that was not controlled, blinded, or randomized. Outside factors such as medications, adherence, and bias may have potentially skewed the data.

Sawicki et al. (2015) evaluated ivacaftor's effect on lung function and whether it slowed the overall decline in lung function and improvement in nutritional status. They did this by matching individuals with G551D taking ivacaftor to Phe508del mutation subjects that did not receive ivacaftor. Data from three previous studies was used, two phase 3 clinical trials by Ramsey et al. in 2011 and Davies et al. in 2013 and the associated open-label 2-year extension study by McKone et al. in 2014 for the G551D subjects. Researchers gathered patients with

G551D (n=189) with an age range of 11 to 34 from the trials and matched them with patients with Phe508del (n=886) mutation with similar ages from the US CF registry data at a 1:5 ratio; All patients were accounted for throughout the study.

After initiation of ivacaftor, ppFEV1 was noted to increase 8.29 percentage points to 76.3 (+/- 1.5) in the treatment group, which was significantly higher than the Phe508del group (68+/- 0.8; $p<0.0001$). This improvement in lung function was sustained over the 3-year period with the difference of ppFEV1 between groups at one year of 9.3 percentage points, and 9.89 percentage points at 2 years. At the end of the study, the overall difference between the two groups was 10.70 percentage points in ppFEV1 ($p<0.001$). Lung function was noted to decline in both groups over the 3-year period, although it was more significant in the Phe508del (-1.72%; SE +/-0.16; $p=0.03$) than the G551D subjects (-0.91).

It is important for one to consider that Sawicki et al. (2015) matches two groups that have different genotypes which could bias and skew the data due to differences in CFTR function. It would be beneficial for future studies to compare within the same mutation to evaluate the overall effect of treatment due to the differences in CFTR protein function and severity of lung disease between these two classes. Limitations also include that they compared US registry data to research data that occurred multi-country, data was not divided out between adults and pediatrics and it was an observational design with limited registry data available. This is important due to differences in culture, climate, genetic variance, bias and skewing the data.

CFTR modulators have mostly been studied in individuals that have ppFEV1 >40%, although CF causes early mortality due to lung disease (Taylor-Cousar, Niknian, Gilmartin & Pilewski, 2016). One of the first studies to evaluate ivacaftor in individuals with severe lung function was completed by Taylor-Cousar, Niknian, Gilmartin and Pilewski (2016). They used

an open-label, non-randomized, single-group, assigned treatment design to evaluate the safety and clinical response of ivacaftor in patients with severe CF lung disease. Subjects could enroll (n=44) if they were 6 years of age or older, had a confirmed diagnosis of CF, at least one G551D-CFTR gene mutation, ppFEV1 <40%, or actively on a lung transplant list.

At the completion of the study, the results indicate that there was a steady increase in ppFEV1 over weeks 2 (n=20; 2.3 percentage points; -9.5 to 10.2), 4 (n=23; 3.6 percentage points; -3.8 to 16.4) and 12 (n=26; 4.8 percentage points; -13.1 to 22.7). At the completion of the study (week 24), 19 subjects had a mean absolute change in ppFEV1 of 5.5 percentage points (-2.6 to 18.4). Treatment response was noted to be variable and frequent pulmonary exacerbations occurred throughout the study. Subjects were also noted to have a slow, steady increase in lung function. This is important to understanding that there may be a delayed response and treatment may need to be continued for a period of longer than 24 weeks to see a treatment effect.

Limitations of the study are that it was an observational study that had no control, blinding or randomization which can increase bias and skew the data. It also had a small sample size, limited number of follow-up (79%) and the researchers did not complete any statistical analysis on the data thus no significant effects were evaluated. Lastly, it may be beneficial to monitor patients with more severe lung disease with a longer study to further evaluate overall effect on lung function and adverse effects.

Theme 3: Lumacaftor with Ivacaftor effect on lung function

A study by Elborn et al. (2016) pooled prespecified data from TRAFFIC and TRANSPORT studies to evaluate the safety and efficacy of lumacaftor-ivacaftor combination therapy. TRAFFIC and TRANSPORT were multinational, randomized, double-blind, placebo-

controlled, parallel-group, 24-week, phase 3 studies completed between April 2013-April 2014. In total, the studies were completed at 187 sites in North America, Australia, and European Union. To be enrolled, subjects had to be aged 12 years or older, have a confirmed diagnosis of CF, be homozygous for Phe508del and have a ppFEV1 of 40-90% at baseline. Elborn et al. (2016) also completed post-hoc analysis for absolute change in ppFEV1 from baseline at each study visit, number (%) of patients that relative ppFEV1 improved at least 10 percentage points, use of IV antibiotics for pulmonary exacerbations, hospitalizations for pulmonary exacerbations, and lastly the number needed to treat to reduce pulmonary exacerbations over 24 weeks. 1449 patients were screened for both trials, n=1122 of these patients were then randomized into the TRAFFIC and TRANSPORT studies with n=1108 (98%) receiving at least one dose of Ivacaftor.

Subjects were randomized into three different study arms and then further stratified for baseline ppFEV1. Individuals that received 600 mg of lumacaftor daily with 250 mg ivacaftor every 12 hours with a baseline ppFEV1 <40% (n=24) had a significant increase in ppFEV1 within the 24 week study when compared to the placebo (n=28; ppFEV1 change 3.7%; 95% CI 0.5 to 6.9; p 0.024). A significant increase in ppFEV1 also occurred with the same treatment in individuals with a ppFEV1 >40% (n=342; least squares mean difference: 3.3; 95% CI 2.3 to 6.9; p=<0.0001) when compared to placebo (n=338). Significant improvement in ppFEV1 also occurred in subjects provided 400 mg of lumacaftor with 250 mg of ivacaftor every 12 hours daily with a baseline ppFEV1 <40% (n=29; least squares mean difference of 3.3; 95% CI 0.2 to 6.4; p=0.036) and ppFEV1 >40% (n=336; least squares mean difference of 2.8; 95% CI 1.7 to 3.8; p <0.0001) when compared to placebo. Treatment groups were then stratified by ppFEV1 <70% and >70% with similar results as the division between <40% and >40%. Individuals with

a baseline ppFEV1 <70% receiving either 600 mg Lumacaftor daily-250 ivacaftor every 12 hours (n=241; ppFEV1 change 3.3%; 2.1 to 4.4; p <0.0001)) or 400 mg lumacaftor-250 mg ivacaftor (n=245; ppFEV1 change 3.3%; 95% CI 2.1 to 4.4; p <0.0001) had a significant increase in ppFEV1 after treatment initiation when compared to the placebo (n=244). A significant change was also noted in subjects with a ppFEV1 of >70% when provided 600 mg lumacaftor daily-250 ivacaftor every 12 hours (n=119; least square mean difference 3.3%; 95% CI 1.3 to 5.4; p 0.002) when compared to placebo (n=109). The only group to not have a significant change in ppFEV1 were the subjects with a ppFEV1 >70% that received 400 mg lumacftor-250 ivacaftor (n=114; least squares mean difference 1.9%; -0.2 to 4.0; p 0.079) over the 24-week study.

When reviewing the trends of the data, it is noted that ppFEV1 improvement peaks around week 15 and is sustained until week 16; however, it starts to decline to week 24 within all treatment groups. Longitudinal data would be helpful to understand if this decline in ppFEV1 continues over time, or if it stabilizes. It would also assist with understanding long-term risks with the medication. Lastly, this study did not separate data between ages, which can potentially cause changes in ppFEV1 to be skewed due to differences in baseline lung function between age groups. When considering use of this study clinically, all treatment groups had similar increases in ppFEV1 after start of the treatment which did not appear to be dependent on baseline ppFEV1. However, this improvement may not be sustained after week 15 and a clinician should monitor ppFEV1 and longitudinal drug tolerance.

Individuals with severe lung disease (ppFEV1 <40%) were studied by Hubert et al. (2017) to evaluate the safety and efficacy of lumacaftor-ivacaftor in this population. They studied the effect that lumacaftor-ivacaftor had on absolute change of ppFEV1 from baseline

after 1 and 3 months along with changes in BMI and adverse events. This multicenter, observational, real life study enrolled individuals older than 18, homozygous F508del with a ppFEV1 <40%. This study included 11 large CF centers and enrolled n=53 subjects with 24% discontinuing the trial due to adverse events.

Results indicated an absolute change of ppFEV1 in all subjects within 1 month of starting lumacaftor-ivacaftor with a mean increase of 2.06 percentage points (n=46; 95% CI 0.04 to 4.09; p 0.086), which was not significant. When the study population was separated for baseline ppFEV1, individuals with a ppFEV1 <30% had a significant increase in ppFEV1 after 1 month (n=18; ppFEV1 change 4.61; 95% CI 0.76 to 8.46; p=0.02), unlike individuals with a baseline ppFEV1 31 to 40% who did not have a significant increase within the same time period (n=28; ppFEV1 change 0.43; 95%CI -1.80 to 2.65; p=0.81). At the completion of the study, pooling of all subjects had a significant improvement in ppFEV1 (n=37; ppFEV1 change 3.19; 95% CI 0.93 to 5.45; p=0.009). Although, when the subjects were separated, individuals with a baseline ppFEV1 <30% had a significant improvement (n=14; ppFEV1 change 5.64; 95% CI 0.54 to 10.74; p=0.03) and those with a ppFEV1 of 31-41% (n=23; ppFEV1 change 1.69; 95% CI -0.38 to 3.77; p=0.13) did not.

This research indicated that treatment may increase ppFEV1, most notably in those with a baseline ppFEV1 of less than 30%. Although, dropout rate was 24% which may indicate that the treatment was not tolerated in this study population. Limitations of the study are that it was an observational study with a small sample size that lasted for a short period (3 months); This could increase bias, skew the data and uncontrolled factors could influence the data in the study. Also, a longer study may help provide additional information on the longitudinal effect of lumacaftor-ivacaftor on ppFEV1 and adverse events with severe lung disease.

Jennings et al. (2017) aimed to evaluate the effect of lumacaftor-ivacaftor in a real-world, clinical review after its approval by the FDA. The study was completed using a retrospective cohort design with patients at the CF Center at Johns Hopkins that had already initiated treatment with lumacaftor-ivacaftor. This was not a controlled trial, it was observational, and all subjects received the study treatment of lumacaftor-ivacaftor. A total of n=116 subjects fit the study criteria with n=41 being aged 12-18. Of the n=116 subjects enrolled, n=20 (17%) discontinued lumacaftor-ivacaftor during the study period.

After treatment initiation, mean ppFEV1 change was not significant (ppFEV1 change 0.11%; range -39 to 20; p=0.9). Jennings et al. (2017) focused on the overall adverse effects of the treatment of lumacaftor-ivacaftor and then compared this to overall ppFEV1. This is helpful clinically because it indicated that individuals with a baseline ppFEV1 <40%, females and age may increase risk for adverse events. Comparing this increased risk to minimal change in ppFEV1 (mean 0.11%) may cause the risk to outweigh the benefit of drug initiation. This study was limited because it was completed at only one center and had an open-label design; this can increase bias and potentially skew the data. It also limits the study size, variability within demographics, geographical region, and care between centers.

PROGRESS was a phase 3, 96-week extension study completed by Konstan et al. (2017) to evaluate long-term treatment with lumacaftor-ivacaftor in individuals older than 12, and homozygous Phe508del. Researchers also evaluated overall lung function decline in a period of 120 weeks in individuals who completed TRAFFIC, TRANSPORT and PROGRESS. The study was designed as a double blind, randomized, parallel-group trial that included 191 sites in 15 countries. A total of n=1030 patients were enrolled from TRAFFIC and TRANSPORT, n=1029

received at least one dose of the study drug, n=850 (82%) completed 72 weeks and n=411 (40%) completed the 96-week extension study.

Subjects were rolled over from TRAFFIC and TRANSPORT and randomized to receive either 400 mg lumacaftor with 250 mg ivacaftor every 12 hours (n=516), or a higher dose of lumacaftor, 600 mg daily, with 250 mg ivacaftor every 12 hours (n=513). Control patients were homozygous Phe508del and gathered from the United States CF Foundation Patient Registry (CFFPR). They were then matched to treatment subjects receiving 400 mg lumacftor-250 ivacaftor every 12 hours by propensity scores. Subjects who were transitioned from the placebo to the study drug, lumacaftor (400 mg) plus ivacaftor (250 mg) every 12 hours (n=176), had an initial increase in absolute ppFEV1 (1.5%; 95% CI 0.2 to 2.9; p=0.0254) at 72 weeks, although this was not sustained by week 96 (0.8%; 95% CI 0.8 to 2.3; p=0.395). Subjects who received the study drug of 400 mg lumacaftor with 250 mg ivacaftor in TRAFFIC and TRANSPORT (n=369) were continued on the treatment during PROGRESS. This group did not have a significant change in absolute change ppFEV1 at week 72 (0.5%; 95% CI -0.4 to 1.5; p=0.2806) or 96 (0.5%; -0.7 to 1.6; p=0.4231). Overall, subjects receiving 400 mg lumacaftor plus 250 mg ivacaftor every 12 hours had an initial increase in absolute ppFEV1, although this was not sustained and a slow decline in ppFEV1 was noted back to baseline. Lung function decline was noted in both the treatment (n=455) and control (n=1588) groups over the two-year extension study. The overall decline in the treatment group was a ppFEV1 loss of -1.33 per year (95% CI -1.8 to -0.85) compared to the control group that had a ppFEV1 loss of -2.29 per year (95% CI -2.56 to -2.03). The difference between the two groups was significant with a p-value of <0.001.

In comparison, subjects who transitioned from the placebo in TRAFFIC or TRANSPORT to 600 mg of Lumacaftor daily with 250 mg of ivacaftor every 12 hours (n=179) had a greater

change in absolute ppFEV1 from baseline at 72 weeks (1.9%; 95% CI 0.6 to 3.2; p=0.0037) which was sustained through 96 weeks (1.6%; 95% CI -0.1 to 3.2; p= 0.0632). However, the subjects who were continued on the treatment (600 mg of lumacaftor daily with 250 mg of ivacaftor every 12 hours (n=368)) from TRAFFIC and TRANSPORT, did not have a significant change in ppFEV1 at weeks 72 (1.2%; 95% CI 0.3 to 2.2; p=0.9682) or week 96 (0.0%; 95% CI -1.1 to 1.1; p=0.9682). This data is consistent with the subjects who received 400 mg lumacaftor plus 250 mg ivacaftor every 12 hours in that overall lung function declined back to baseline with prolonged use.

This study provides longitudinal data on the safety and efficacy of lumacaftor-ivacaftor in homozygous Phe508del patients. Most notably, patients who receive lumacaftor-ivacaftor will have an initial increase in ppFEV1, although this is not sustainable over time. When compared to the control population, both were noted to have a steady decline in lung function over the two-year period. Limitations of the study are that the data was not separated between age groups. This is important due to differences in overall baseline lung function between age groups and lung disease progression as an individual ages, which could skew the results. It is also important to note that only 40% of the initial study participants completed the full 96-week extension study. A clinician needs to consider the possibility that this may be related to treatment intolerance and outweigh the risk versus the benefits of initiating this medication due ppFEV1 changes not being sustainable over time.

A research study by Taylor-Cousar et al. (2018) evaluated the safety and efficacy of lumacaftor-ivacaftor in individuals with advanced lung disease. The study design was a phase 3b, prospective, open-label, 24-week clinical study conducted at six sites in the United States between February 19, 2015 and October 3, 2016. Subjects could enroll in the study if they were

homozygous F508del, older than 12 years of age and had advanced lung disease (ppFEV1 <40%). Once enrolled, all subjects received 400 mg lumacaftor every 12 hours in combination with 250 mg of ivacaftor every 12 hours (n=28). Subjects who experienced adverse events, could be provided a half dose of the study medication for seven days, 200 mg lumacaftor with 125 mg ivacaftor every 12 hours, to aid overall tolerance of the medication (n=18). The goal was to enroll 100 to 200 subjects, although they were only able to recruit 46 with 35 (76%) completing all 24 weeks of the trial.

After initiation of lumacaftor-ivacaftor, there was an initial decline in ppFEV1 by day 15 (95% CI: -1.7 (-3.2, -0.1)), although by week 4 ppFEV1 trended upward to just below baseline (95%CI -0.4 (-1.6 to 0.8)). This trend upward continued and by week 8, ppFEV1 was just above baseline (95% CI 0.4 (-1.2 to 1.6)) and this was sustained through week 16 (95% CI 0.4 (-1.2 to 2.0)). ppFEV1 then dropped slightly below baseline at week 24 (95% CI: -0.4 (-1.9, 1.1)). This may indicate that lumacaftor-ivacaftor does not have a significant effect on ppFEV1 in individuals with severe lung function (ppFEV1 <40%).

Clinically, the effect of lumacaftor-ivacaftor provides small benefit especially when considering the overall harm of the medication. The study by Taylor-Cousar, et al. (2018) indicated that patients had more respiratory events and adverse effects than what had been noted in previous trials in individuals with ppFEV1 40-90%. Limitations of the study are that it was completed for only 24 weeks, had a small sample size and was observational. Researchers also did not divide out the overall effect of treatment between the subjects that received a half dose compared to a full dose of the study medication or between age groups (12 to 18 versus >18). It would be helpful to understand how the dosing difference and age may affect treatment tolerance and changes in ppFEV1 from baseline.

TRAFFIC and TRANSPORT were phase 3, multinational, randomized, double-blind, placebo-controlled, parallel-group designed trials that were completed by Wainwright, et al. (2015) in follow-up to phase 2 trials that suggested that lumacaftor-ivacaftor have effects on CFTR activity. The goal of the study was to evaluate the safety and efficacy of lumacaftor-ivacaftor with two different doses in patients aged older than 12 with CF that were homozygous for Phe508del. A total of n=1122 subjects entered the trial with n=559 enrolled in TRAFFIC and n=563 enrolled in TRANSPORT; n=1108 received at least one dose of the study drug or placebo. At the end of the trial, n=344 (93.2%) of the 400 mg lumacaftor-250 mg ivacaftor group, n=348 (94.6%) 600 mg lumacaftor-250 mg ivacaftor, and n=362 (97.6%) of the placebo group completed the 24-week trial.

Subjects were randomly assigned to one of three treatment arms: 600 mg lumacaftor daily plus 250 mg ivacaftor every 12 hours, 400 mg lumacaftor plus 250 mg ivacaftor both taken every 12 hours or lumacaftor-matched placebo taken every 12 hours in combination with ivacaftor-matched placebo every 12. Subjects within the TRAFFIC study that received 600 mg lumacaftor-250mg ivacaftor (n=183) had an absolute change in ppFEV1 of 4.0 percentage points (95% CI 2.6 to 5.4; $p < 0.001$) which showed a greater effect then subjects receiving 400 mg lumacaftor-250 mg ivacaftor every 12 hours (n=182; absolute increase ppFEV1: 2.6 percentage points; 95% CI 1.2 to 4.0; $p < 0.001$). Subjects enrolled in the TRANSPORT study had a significant change in ppFEV1 in both treatment groups, 600 mg lumacaftor-250mg ivacaftor (n=185; absolute change ppFEV1: 2.6 percentage points; 95% CI 1.2 to 4.1; $p < 0.001$) and 400 mg lumacaftor-250 mg ivacaftor every 12 hours (n=187; absolute ppFEV1 3.0 percentage points; 95% CI 1.6 to 4.4; $p < 0.001$). The data from the two studies were then pooled and indicated that both treatments had a significant change, although the individuals that received 600 mg

lumacaftor-250mg ivacaftor (n=368; 3.3 percentage points; 95% CI 2.3 to 4.3; p <0.001) had a greater effect then subjects receiving 400 mg lumacaftor-250 mg ivacaftor every 12 hours (n=369; absolute ppFEV1 2.8 percentage points; 95% CI 1.8 to 3.8; p <0.001). It does appear that the overall change in ppFEV1 occurred by week 15, peaked by week 16 and started to slowly decline by week 24 in the 600 mg lumacaftor-250 mg ivacaftor group. Although, the decline was not significant and remained above baseline ppFEV1. It is noted that ppFEV1 peaked earlier, by week 8, in the 400 mg lumacaftor-250 mg ivacaftor every 12-hour group, which then had a steady decline.

Clinically, ppFEV1 may improve after initiation of lumacaftor-ivacaftor. However, the improvement appears to be acute and starts to decline after week 8. It is difficult to know if age affects the overall treatment effect due to exclusion of the raw data between age groups (12-18 and >18). There was limited information provided in one figure which depicted the absolute change in ppFEV1. Overall, by looking at the comparisons one can gather the treatment effect is overall equal and favors treatment in both age groups, although changes in ppFEV1 were more variable in the subjects aged 12-18 (n=186; range 0.5-6%) than the adults (>18; n= 523; range 2-5%). It would be helpful to understand how pooling this data may have skewed the overall effect on ppFEV1 due to differences in baseline lung function between ages. The length of the study is also a limitation in that at week 24 lung function started to decline, a longer study would help a clinician understand if this trend will continue with prolonged use of the medication. Thus, a longitudinal study would be helpful to understand the long-term effect of the medication on lung function in individuals homozygous Phe508del.

Theme 4: Tezacaftor with Ivacaftor effect on lung function

A phase 2, randomized, placebo-controlled, double blind, multicenter study by Donaldson, et al. (2018) used a multiple ascending dose and parallel-arm design to evaluate the safety and efficacy of tezacaftor monotherapy and tezacaftor-ivacaftor combination therapy. They enrolled individuals with F508del/F508del-CFTR (18 years and older) or F508del/G551D-CFTR (12 years and older) mutations that had a baseline ppFEV1 of 40-90%. The study was conducted at 37 CF centers in the United States, Canada, Germany, and the United Kingdom from February 2012 to March 2014. A total of n=190 subjects entered the trial and were randomized at a 4:1 ratio with n=185 (97.4%) completing the full study (28 weeks) with a 28-week washout period at the completion of the study.

Results indicate that the absolute change in ppFEV1 from baseline in the placebo group was -0.14% (n=26; 95% CI -2.0 to 1.8). Subjects receiving monotherapy of tezacaftor during the dose escalation phase (n=34), did not have a significant change in ppFEV1 from baseline when provided 10 mg (ppFEV1 change: 3.49; 95% CI 0.2 to 6.8), 30 mg (ppFEV1 change 1.63; 95% CI -1.5 to 5.0), 100 mg (pFEV1 change: 1.60; 95% CI -2.0 to 5.0) or 150 mg (ppFEV1 change: 2.54; 95% CI -0.5 to 5.5). There was a significant effect on absolute change of ppFEV1 with duo therapy (n=71), most notable when higher doses of tezacaftor were combined with ivacaftor (150 mg every 12 hours). The doses that had a significant effect were: 100 mg tezacaftor-150 ivacaftor (3.75%; 95% CI 2.0 to 6.0; $p < 0.05$) and 150 mg tezacaftor-150 mg ivacaftor (3.61%; 95% CI 2.0 to 6.0; $p < 0.05$). The greatest improvement being in the 100 mg tezacaftor-150 mg ivacaftor group.

Clinically, duo-therapy with tezacaftor-ivacaftor had more improvement in ppFEV1 than monotherapy with tezacaftor in individuals that are homozygous Phe508del and heterozygous Phe508del and G551D. Due to the short length of the study, it would be difficult to recommend

duo therapy in this population. It would be beneficial to evaluate a longitudinal study to provide additional information on the sustainability of improved ppFEV1 and safety. It should also be noted that this was a phase 2 study that focused more on the safety of the medication and less on the efficacy. Thus, it did not separate out individuals between baseline ppFEV1 or age. It would be helpful to understand if the effect of treatment is dependent on age or baseline ppFEV1.

Rowe et al. (2017) studied whether tezacaftor-ivacaftor combination would aid CFTR protein function in individuals aged 12 years and older that were heterozygous Phe508del with a second allele that had a residual function mutation and baseline ppFEV1 between 40 and 90%; Researchers also sought to ensure the safety and efficacy of the medication. This was a phase 3, randomized, double-blind, placebo-controlled crossover trial that had 2-periods and three interventions. It was conducted at 86 sites in Australia, Europe, Israel, and North America from March 27, 2015 to February 16, 2017. A total n=248 subjects enrolled in the trial and underwent randomization with n=234 (95%) completing both intervention periods for a total of 481 evaluation periods.

Each patient received two of the three therapy regimens. These regimens were: 100 mg tezacaftor (1/day) with 150 mg ivacaftor (every 12 hours) combination therapy, monotherapy of 150 mg ivacaftor (every 12 hours) or placebo for eight weeks with an eight-week washout period between treatments. Three comparisons were made within the treatment groups. The first comparison was monotherapy of ivacaftor (n = 156) versus placebo (n= 161) with absolute change ppFEV1 increasing by 4.7 percentage points (95% CI 3.7 to 5.8). The second comparison was between duo-therapy of tezacaftor-ivacaftor (n=161) and placebo (n =161) which had a significant absolute change in ppFEV1 from baseline of 6.8 percentage points (95% CI 5.7 to 7.8; p=<0.001). The last comparison was between the duo therapy of tezacaftor-ivacaftor

(n=161) and monotherapy of ivacaftor (n=156) with a significant absolute change in ppFEV1 of 2.1 percentage points (95% CI 1.2 to 2.9; p = <0.001). The largest treatment effect on ppFEV1 was found in the duo-therapy treatment of tezacaftor-ivacaftor by day 15 and was sustained through 8-weeks of treatment. Both duo-therapy with tezacaftor-ivacaftor and monotherapy of ivacaftor alone showed significant improvement of ppFEV1 from baseline at day 15, although duo-therapy had a larger increase (5.5% versus 4%; p <0.05).

The data was then further stratified to evaluate the effect of age, absolute ppFEV1 (<40%, 40-70%, >70%) and mutation when receiving each treatment arm or the placebo. Subjects aged <18 had a greater improvement in ppFEV1 with tezacaftor-ivacaftor (absolute ppFEV1 12%; 95% CI 9.3 to 14.8) and ivacaftor alone (absolute ppFEV1 8.0%; 95% CI 5.2 to 10.7) then those aged >18 (tezacaftor-ivacaftor: absolute ppFEV1 6%; 95% CI 4.9 to 7.0; ivacaftor: absolute ppFEV1: 4.2%; 95% CI 3.1 to 5.3). Absolute change in baseline ppFEV1 was similar with both treatments in individuals with a ppFEV1 of <40% (tezacaftor-ivacaftor: 4.4%; 95% CI 1.1 to 7.8; ivacaftor: 4.4%; 95% CI 0.9 to 7.9). Subjects with a baseline ppFEV1 of 40-70% had a greater improvement with tezacaftor-ivacaftor (absolute ppFEV1: 6.4%; 95% CI 5.1 to 7.8) then ivacaftor alone (absolute ppFEV1: 4.3%; 95% CI 2.9 to 5.7). This was also noted in those with a baseline ppFEV1 >70% (tezacaftor-ivacaftor: absolute change ppFEV1 8.2%; 95% CI 6.4 to 10.1; ivacaftor: absolute ppFEV1: 5.7%; 95% CI 3.8 to 7.6). Lastly, the residual function mutation effected the overall change of absolute ppFEV1 from baseline. Class V noncanonical splice mutations had a greater improvement in ppFEV1 with tezacaftor-ivacaftor (absolute change ppFEV1: 7.4%; 95% CI 6.0-8.7) then ivacaftor (absolute change ppFEV1: 5.4; 95% CI 4.1-6.8). This was also noted with Class II to IV residual function mutations (tezacaftor-

ivacaftor: absolute change ppFEV1 5.9%; 95% CI 4.2 to 7.5; ivacaftor: absolute change ppFEV1: 3.6%; 95% CI 1.9 to 5.2).

Overall, duo-therapy of tezacaftor-ivacaftor had a greater improvement on absolute ppFEV1 when compared to monotherapy of ivacaftor and placebo. This is noted when comparing for age (>18, <18), overall baseline ppFEV1 (<40%, 40-70%, >70%) and mutation type (class V noncanonical splice mutations and Class II to IV residual function mutations). A limitation of the study was the length of each treatment arm was short at only 8 weeks. It would be beneficial to extend the treatment arms for a longer period to further determine if the absolute improvement of ppFEV1 is sustainable over years and not only 8 weeks.

Taylor-Cousar et al. (2017) aimed to evaluate the safety and efficacy of tezacaftor, a CFTR corrector, when combined with ivacaftor, a CFTR potentiator in homozygous Phe508del individuals. This study was designed as a phase 3, randomized, double blind, multi-center, placebo-controlled, parallel-group trial. It was conducted at 91 sites in the United States, Canada, and Europe from January 30, 2015 to January 20, 2017. To enroll in the study, subjects had to have the criteria of homozygous Phe508del, 12 years of age or older and have a ppFEV1 between 40-90% and stable disease, as analyzed by the investigators. Subjects were randomized by a 1:1 ratio to receive either combination therapy of 100 mg tezacaftor-150 mg ivacaftor (1/day) or placebo for 24 weeks. A total of 510 subjects enrolled in the study with a total of 509 receiving at least one dose of the study drug and 475 subjects completed the 24 weeks (95% follow-up; n=235 study drug and n=240 placebo). Most subjects that discontinued the trial (n=15) did so due to adverse effects (7 tezacaftor-ivacaftor; 8 placebo).

After receiving tezacaftor-ivacaftor for 24 weeks, there was a significant change in ppFEV1 (n=251; least squares mean ppFEV1 change 4.0%; 95% CI 3.1 to 4.8; p=<0.001)

indicating a treatment effect when compared to the placebo (n=258). When absolute change from baseline of ppFEV1 was compared at day 15, and weeks 4, 8, 12, 16, and 24 the largest improvement was noted at day 15 of around 3% and this was sustained throughout the study period.

This study would be helpful if it provided more longitudinal data, it was only for 24 weeks. Although, subjects did have the option to join a 96-week extension study after completion; this study data is not yet available. When considering the data, Taylor-Cousar et al. (2017) did not divide out the data for individual age groups (<18 versus >18), the data reported was for the total cohort. This is important because individuals aged 12-18 may have better baseline lung function which may skew the data. Clinically, tezacaftor-ivacaftor has a more sustainable increase in ppFEV1 at week 24 when compared to previous trials of lumacaftor-ivacaftor in individuals homozygous Phe508del. One can also gather from this study that the improvement between tezacaftor-ivacaftor and the placebo is significant. Individuals in the placebo group had an overall decline in lung function at week 16 and those in the treatment group had sustained lung function above baseline.

Theme 5: Triple therapy's effect on lung function

The addition of a corrector to the previous corrector-potentiator combination was studied by Heijerman et al. (2019) to evaluate if this would improve processing, trafficking and restore CFTR protein in individuals with F508del mutation; This was completed by using elexacaftor (VX-445) in combination with tezacaftor and ivacaftor. This phase 3, multicenter, randomized, double blind, active-controlled trial was completed at a total of 44 sites in Belgium, the Netherlands, the United Kingdom, and the USA. Subjects could enroll in the study if they had a confirmed diagnosis of CF, were homozygous F508del mutation, aged 12 years and older and

had a ppFEV1 between 40-90% which was stable, as judged by the researchers. There was a total of 113 subjects enrolled in the study with 107 (94%) receiving being randomly assigned and completing the 4 weeks of treatment.

Subjects were randomly assigned at a 1:1 ratio by an interactive web response system to receive triple therapy (200 mg Elexacaftor-100 mg Tezcaftor-150 mg Ivacaftor (every 12 hours)), combination therapy (100 mg Tezcaftor-150 mg Ivacaftor (every 12 hours)) or a placebo. Randomization was further stratified by dividing the groups by ppFEV1 (>70% or <70%) and age (>18 or <18). Subjects that received tezacaftor-ivacaftor (n=52), had an absolute change in ppFEV1 of 0.4% (-1.4 to 2.3) which was less than the group that received elexacaftor-tezacaftor-ivacaftor (n=55; absolute change ppFEV1: 10.4%; 8.6 to 12.2). When these two groups were compared, the least squares mean difference was 10.0% (7.4 to 12.6; $p < 0.0001$) indicating that treatment with elexacaftor-tezacaftor-ivacaftor had a significant effect over tezacaftor-ivacaftor.

Clinically, this study shows that ppFEV1 may be improved in individuals with F508del when provided triple therapy (two correctors and one potentiator). Although, this study was limited in that it was only 4 weeks long. Results at week 4 indicate that ppFEV1 continues to increase, it would be important to understand if this continues and if it is sustainable over time. Subjects from this study could choose to extend the study to 96 weeks which would provide more longitudinal data compared to 4 weeks, although results of the extended study are not yet available.

One of the first trials on VX-445 (elexacaftor) was completed by Keating et al. (2018) with the goal to examine the effects of VX-445 when combined with another processor (tezacaftor) and potentiator (ivacaftor) on CFTR function at the cell surface. They hypothesized

that by providing all three, CFTR function would be further improved. This study was completed at 38 sites in the United States, Netherlands, Belgium, and Australia and enrolled individuals that had one or two F508del alleles that were aged 18 years and older. The study was designed as a three-part, randomized, double-blind, placebo or active control, parallel group, dose ranging, phase 2 trial from July 2017 through March 2018. The study enrolled n= 123 subjects with n= 119 completing the full trial.

Analysis was completed based on their genetic characteristics and study group. The first group, F508del combined with a minimal function allele, was subdivided into four groups: a triple placebo, 50 mg VX-445+tezacaftor-ivacaftor, 100 mg VX445+tezacaftor-ivacaftor and 200 mg VX-445+tezacaftor-ivacaftor. When placebo groups are compared to treatment groups, a significant improvement was noted in ppFEV1 with all treatment groups. Subjects with one F508del and a minimal function allele provided 50 mg VX-445+tezacaftor-ivacaftor had a significant change in ppFEV1 (absolute change 11.1% +/-2.1; 95% CI 7.0 to 15.3; $p<0.001$). When the VX-445 was increased to 100 mg and provided with tezacaftor-ivacaftor to F508del with a minimal function allele absolute change in ppFEV1 was 7.9% +/-1.4 (95% CI 5.1 to 10.6; $p <0.001$). The largest effect was noted with the 200 mg VX-445 + tezacaftor-ivacaftor when provided to F508del combined with a minimal function allele (absolute change ppFEV1 13.8% +/-1.4; 95% CI 10.9 to 16.6; $p <0.001$). The second group, those homozygous F508del, were split into two groups, a placebo+tezcaftor-ivacaftor and 200 mg VX-445+tezcaftor-ivacafor. Subjects who received the treatment, 200 mg VX-445+tezcaftor-ivacafor, had a significant change in ppFEV1 from baseline (absolute change 11.0% +/-1.5; 95% CI 7.9 to 14.0; p value <0.001).

This study by Keating et al. (2018) suggests that individuals with one or two F508del alleles may have a significant benefit from baseline on ppFEV1 when taking 200 mg VX-445-tezcaftor-ivacaftor. When comparing all groups, these two groups had the largest noted treatment effect which was sustained throughout the treatment trial. This indicates that using two correctors and potentiator may assist in improving CFTR cell surface function in individuals with one or two F508del alleles and have a positive effect on lung function over 4 weeks. Unfortunately, this study was only completed for 4 weeks. A longer study would have provided more information on the longitudinal effect of the drug and whether the notable increase in ppFEV1 was sustained and safe.

A phase 3, randomized, multi-centered, double-blind placebo-controlled study by Middleton et al. (2019) evaluated the efficacy and safety of elexacaftor-tezacaftor-ivacaftor in patients heterozygous for Phe508del. They compared the treatment group to the placebo to see if elexacaftor-tezacaftor-ivacaftor had significant effects on outcomes from baseline. To enroll in the study, subjects had to be heterozygous for Phe508del and a minimal function mutation, aged 12 years and older with cystic fibrosis, a ppFEV1 of 40 to 90% and stable disease during the 28 day screening period before being provided the placebo or treatment. Subjects were enrolled from 115 sites in 13 countries with n=405 patients undergoing randomization and n=403 (99%) receiving at least one dose of trial regimen (200 triple therapy and 203 in placebo).

Subjects were randomly assigned in a 1:1 ratio to receive either elexacaftor (200 mg once daily) in triple combo with tezacaftor (100 mg once daily) and ivacaftor (150 mg every 12 hours) or matched placebo. The groups were then stratified based on ppFEV1 (<70% or >70%), age (>18 or <18) and sex. Subjects that received elexacaftor-tezacaftor-ivacaftor had an absolute change in ppFEV1 of 13.6% (95% CI 12.4 to 14.8) which was significant when compared to the

placebo group with an absolute change in ppFEV1 of -0.2% (95% CI -1.3 to 1.0; p=<0.001). The difference between the two groups was an absolute change ppFEV1 of 13.8% (95% CI 12.1 to 15.4). When subjects continued triple therapy treatment for 24 weeks, ppFEV1 improvement was sustained with an absolute change of 13.9% (95% CI 12.8 to 15.0) versus placebo that had and absolute change in ppFEV1 of -0.4% (95% CI -1.5 to 0.7; p=<0.001) noting a significant difference with treatment. Difference between the treatment and placebo groups at 24 weeks was an absolute change in ppFEV1 of 14.3 percentage points (95% 12.7 to 15.8). The improvement in ppFEV1 was noted as early as week 4 and was sustained through week 24 (p <0.001; CI: 12.1 to 15.4) in all subgroups, including those with a ppFEV1 <40% at baseline. Treatment appears to have similar effects on ppFEV1 between age groups with subjects aged 12 to 18 (n=99) having an absolute change of ppFEV1 at 4 weeks of 13.8% (95% CI 10.0 to 17.5) and those > 18 (n=278) had similar improvement in ppFEV1 of 13.6% (95% CI 11.9 to 15.8).

Clinically, this study is important because it showed a significant change in ppFEV1 in individuals that are heterozygous Phe508del with triple therapy. This occurred in both pediatric and adult patients with a similar average. However, the study was limited due to it lasting for only for 24 weeks. A longitudinal study would help provide further information on the sustainability of ppFEV1 and safety with triple therapy. Lastly, the study was double blinded, although Middleton, et el. (2019) did not discuss how they kept the researchers and subject's allocation concealed which reduces the reproducibility and potentially may bias the study.

Discussion

Ivacaftor monotherapy effect on lung function

Monotherapy with ivacaftor was shown to increase ppFEV1 in individuals with at least one G551D allele, non-G551D gating mutations, Gly-Asp-CFTR mutation and ARG117HIS (Kirwan et al., 2019; Konstan et al., 2015; Sawicki, et al., 2015; Guimbellot et al., 2019; De

Boeck et al., 2014; Hubert et al.; 2018; McKone et al., 2014; Moss et al., 2015). ARG117HIS mutation had less improvement in ppFEV1 than the other mutations when provided ivacaftor which may be related to this mutation progressing to more severe lung disease in adult life (Moss et al., 2015). Lastly, ivacaftor's effects appear to be age dependent. In individuals with non-G551D mutations, adults aged greater than 18 had an average of 10% improvement in ppFEV1 over individuals aged 6-11 (Guimbellot et al., 2019). This differs from those with at least one G551D mutation and Gly-Asp-CFTR in that the adolescents (aged 11-18) had the greatest improvement when compared to the adults and children aged 6 to 11 (Hubert et al., 2018; Kirwan et al., 2019). Unfortunately, many studies do not divide the data out between ages which could skew the data.

Individuals with severe lung disease (ppFEV1 <40%) and at least one G551D allele may have improvement in lung function once started on ivacaftor (Barry et al., 2014; Taylor-Cousar et al., 2016). Although, a large variance in treatment response between subjects was noted (See Appendix A, Table A3). Response to treatment in severe lung disease was noted to have a slow, steady increase in lung function unlike individuals with ppFEV1 of >40%, in which they had a more immediate rise in ppFEV1 after initiation; The improvement in ppFEV1 may not occur until 180 days after the treatment has started (Barry et al., 2014). It is important to note that individuals with Gly-Asp-CFTR mutation and ppFEV1 <40% did not have a significant improvement in lung function, although the sample size was small and more studies would be helpful in understanding it's overall effect in this population (n=9)(Hubert et al., 2018).

Ivacaftor appears to improve lung function and ppFEV1 in individuals by improving muccocilliary clearance in the lung (Rowe et al., 2014). This may correlate with the improvement noted with CT imaging which indicated reduced peribronchial thickening and

mucous plugging (Ronan et al., 2018). Due to the changes noted on CT, this may be an alternative way to evaluate lung function if spirometry cannot be completed (Ronan et al., 2018). Although, more studies discussing the correlation between lung function (ppFEV1) and change in CT scan would be warranted.

Lumacaftor with Ivacaftor effect on lung function

Duo-therapy of lumacaftor and ivacaftor was studied most in individuals with at least one Phe508del allele. When provided to individuals with a baseline ppFEV1 between 40-90%, ppFEV1 improved after initiation of lumacaftor-ivacaftor, although this was not sustained and was noted to trend down (See Appendix B, Table B1; Elborn et al., 2016; Konstan et al., 2017; Wainwright et al., 2105). It is notable that respiratory events and adverse events were noted in many of the studies along with high-dropout rates (Hubert et al., 2017; Jennings et al., 2017; Konstan et al., 2017; Taylor-Cousar et al., 2018). A clinician needs to monitor for treatment intolerance and outweigh the risk versus the benefits of initiating this medication due ppFEV1 changes not being sustainable over time. Unfortunately, the studies did not differentiate between ages, so an age dependent effect is unknown. The studies also only evaluated patients who were homozygous Phe508del and thus is would be beneficial to evaluate the effect of ivacaftor-lumacaftor in individuals heterozygous Phe508del for a treatment difference.

Tezacaftor with ivacaftor effect on lung function

Tezacaftor-ivacaftor is a duo-therapy treatment that was studied for use in individuals with at least one Phe508del allele. Clinically, tezacaftor-ivacaftor has a more sustainable increase in ppFEV1 at week 24 when compared to previous trials of lumacaftor-ivacaftor and ivacaftor or tezacaftor alone in individuals homozygous Phe508del (Taylor-Cousar et al., 2017; Rowe et al., 2017; Donaldson). There does seem to be a difference in response to treatment

between ages, with those aged less than 18 having a larger improvement (See Appendix C, Table C1), although further research is needed due to only one study evaluating age dependent changes (Rowe et al., 2017). Lastly, there may be a difference in response between those that are heterozygous Phe508del compared to those that are homozygous Phe508del (See Appendix C, Table C1). Individuals who are heterozygous Phe508del may have a larger improvement in ppFEV1 than those homozygous Phe508del (Donaldson et al., 2018; Rowe et al., 2017; Taylor-Cousar et al., 2017). Although, one needs to consider the class of the second allele and thus further research is needed to evaluate a difference in treatment.

Triple therapy's effect on lung function

The newest medication trials with individuals heterozygous or homozygous for Phe508del has been with triple therapy of elexacaftor-tezacaftor-ivacaftor. This combination medication appears to have the greatest effect on ppFEV1 with this mutation when compared to both tezacaftor-ivacaftor and lumacaftor-ivacaftor. For example, elexacaftor-tezacaftor-ivacaftor improved ppFEV1 around 10-13% on average (Heijerman et al., 2019; Keating et al., 2018; Middleton et al., 2019) compared to 3.4-12% with tezacaftor-ivacaftor (Donaldson et al., 2018; Rowe et al., 2017; Taylor-Cousar et al., 2017) and 0.5-3.3% with lumacaftor-ivacaftor (Elborn et al., 2016; Jennings et al., 2017; Konstan et al., 2017; Wainwright et al., 2015) in subjects with a baseline ppFEV1 between 40-90%. It is also important to note that the treatment effect appears to be sustainable over 24 weeks, unlike lumacaftor-ivacaftor in which the treatment effect declines starting around weeks 8 to 15 (Middleton et al., 2019; Elborn et al., 2016; Jennings et al., 2017; Wainwright., 2015). Use of elexacaftor-tezacaftor-ivacaftor in individuals heterozygous Phe508del (Keating et al., 2018; Middleton et al., 2019) may have a greater improvement in ppFEV1 than those homozygous Phe508del (Keating et al., 2018; Heijerman et al., 2019). Lastly, the effect of this medication does not appear to be age dependent but has a

consistent improvement between age groups (See Appendix D, Table D2; Middleton et al., 2019). Although, more studies are needed.

Applicability to Clinical Practice

CFTR modulators are a relatively new medications that can have positive effects on an individual with CF. It is important for providers to know and understand what these medications are and how they may improve a patient's respiratory function, BMI, fat absorption and quality of life.

Ivacaftor, is used as monotherapy in individuals with class III and class IV mutations such as: G551D allele, non-G551D gating mutations, Gly-Asp-CFTR mutation and ARG117HIS. After initiation, ppFEV1 may rise and be sustained over a one to two-year period in individuals with a baseline ppFEV1 >40% (Hubert et al., 2018; Kirwan et al., 2019). On the other hand, individuals with ppFEV1 <40% may have a slower rise in ppFEV1 after initiation, thus this may need to be trialed for at least 180 days to show an effect (Barry et al. 2014). Clinicians should monitor the overall effect of the medication by use of ppFEV1 prior to initiation and throughout treatment. It is also important to monitor for any side effects of the treatment and to evaluate if the continued use of the medication is efficacious to the patient.

There are three options of CFTR modulators that can be used in individuals with a class II mutation (at least one Phe508del allele). Of the three, elexacaftor-tezacaftor-ivacaftor was noted to have the most beneficial effects on ppFEV1 after initiation which was sustained when compared to lumacaftor-ivacaftor and tezacaftor-ivacaftor. The improvement was noted within the first 4 weeks of treatment (Middleton et al., 2019). However, more longitudinal studies with elexacaftor-tezacaftor-ivacaftor are needed to ensure that the ppFEV1 improvement is sustained over years and not months and that the medication remains safe over a prolonged period. A

clinician should understand that if lumacaftor-ivacaftor is initiated an acute rise in ppFEV1 may be seen, although this may not be sustained, and may trend down around week 16 (Wainwright et al., 2015). Treatment differences between whether a patient is heterozygous or homozygous Phe508del may be seen with any of the three medications (See Appendix B, C, and D).

It is also important to recognize that CFTR medication effects may be age dependent. Individuals aged 11-18 years old were noted to have a larger increase in ppFEV1 when compared to adults (>18 years old) with ivacaftor monotherapy (Hubert et al., 2018; Kirwan et al., 2018). Unfortunately, studies with elexacaftor-tezacaftor-ivacaftor, tezacaftor-ivacaftor, and lumacaftor-ivacaftor have not evaluated the age dependent effect. Thus, more studies are needed to evaluate age dependent changes and a clinician needs to be aware that different aged individuals may have variable responses to treatment. Lastly, baseline ppFEV1 did not appear to have an impact on response to treatment. Individuals with either severe lung function (ppFEV1 <40%) or normal lung function (ppFEV1 >40%) were noted to have an increase in ppFEV1 after initiation of CFTR modulators, although individuals with severe lung function may have more side effects than those with normal lung function (Taylor-Cousar, 2016).

In conclusion, CFTR modulators may have positive effects on lung function with use of ppFEV1 for monitoring. Initiation of these medications may help reduce the effects that chronic inflammation has on the lungs which may improve lung function (Ronan et al., 2018). However, continued research on age dependent effects, longitudinal studies, response to treatment and efficacy of treatment are needed.

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Appendix A

Table A1
Ivacaftor monotherapy: Baseline ppFEV1 40-90% change in ppFEV1 (CI)

Study	**Mutation**	**Time Frame** **Adults >18**	**Time Frame** **Pediatrics Aged 6-17**	**Time Frame** **Pediatrics Aged 6-12**	**Time Frame** **Pediatrics Aged 12-18**
Guimbellot et al. (2019)	Non-G511D gating mutation	6 months 16.4 (1.1, 31.8); 63.1%	6 months 6.1 (-4.1, 16.2; p=0.2058); 94.6%		
Hubert et al. (2018)	Gly-Asp-CFTR	Year 1: 7.0 +/- 12.5 (p 0.009) Year 2: 5.5 +/- 13.9 (p NS)		Year 1: 7.3 +/- 19.0 (p NS) Year 2: 6.1 +/- 18.4 (p NS)	Year 1: 12.5 +/- 11.5 Year 2: 12.3 +/- 6.3 (p 0.053)
Kirwan et al. 2019	G551D	7.4 (4.9 to 9.9) *a decline occurred after year 3 of -1.74% (-3.1 to -0.4)		2.26 (71 to 91.8)	9.1 (4.6 to 13.6)
McKone et al. (2014)	Gly551Asp-CFTR			ENVISION Day 48: 8.8 (SD 12.5) Day 96: 10.5 (SD 11.5)	
Moss et al. (2015).	ARG117HIS		24 weeks 4.5 (1.15 to 8.78; p 0.01)	24 weeks -2.8 (-11.96 to -0.71; p 0.03)	

Ronan et al., 2019	G551D	12.0 (p <0.01)

Table A2
Ivacaftor monotherapy: Articles that pooled age related data change in ppFEV1 (CI)

Article	**Mutation**	**Time Frame** **All Subjects >6 years old**	**Time Frame** **All subjects >11 years old**
De Boeck et al., 2014	Non-G551D gating mutations	2 weeks 7.23 8 weeks 8.13 24 weeks 13.5 (-6.9 to 36.5)	
Konstan et al., 2015	G551D	Lower vs placebo 2.29 (0.40 to 4.19; p 0.0179) Middle vs placebo 9.66 (7.82 to 11.49; p <00001) Upper vs placebo 20.73 (18.5 to 22.96; p <0.0001)	
McKone et al., 2014	Gly551Asp-CFTR	STRIVE (adults/adolescents) Day 48: 9.4 (SD 8.5) Day 96: 9.5 (SD 11.2)	
Ronan et al., 2019	G551D	10.3 (p <0.001)	
Rowe et al., 2014	G551D	1 month 6.7 (5.2 to 8.3; p <0.001) 3 months	

		5.4 (4.0 to 6.7; p <0.001) <u>6 months</u> 6.7 (4.9 to 8.5; p <0.001)		
Sawicki et al., 2015	G551D			<u>1 Year</u> 9.90 <u>2 Year</u> 9.89 <u>3 Year</u> 10.70 (These are the differences between treatment and placebo)

Table A3
Ivacaftor monotherapy: baseline ppFEV1 <40% change in ppFEV1 (CI)

Article	**Mutation**	**Time Frame** **Placebo**	**Time Frame** **Adults >18**	**Time Frame** **All Subjects (>6 years old)**
Barry et al., 2014	G551D	<u>Average 237 days</u> 0.6 (-2.1 to 2.8)	<u>Average 237 days</u> 3.8 (0.2 to 7.7; p 0.009)	
Hubert et al. 2018	Gly-Asp-CFTR			<u>Year one</u> 5.0 +/- 8.8 (p 0.126) <u>Year two</u> 4.8 +/- 6.8 (p 0.069)
Taylor-Cousar et al., 2016	G551D			<u>2 weeks</u> 2.3 (-9.5 to 10.2) <u>4 weeks</u> 3.6 (-3.8 to 16.4) <u>12 weeks</u>

	4.8 (-13.1 to 22.7) 24 weeks 5.5 (-2.6 to 18.4)

Appendix B

Table B1
Lumacaftor-Ivacaftor: baseline ppFEV1 40-90% change in ppFEV1 (CI)

Article	**Mutation** **Medication Dose**	**Time Frame** **Age: >12**
Elborn et al., 2016	Homozygous Phe508del Dose: 600 mg LUM-250 mg IVA	24 weeks 3.3 (2.3 to 4.4; p <0.0001)
Elborn et al., 2016	Homozygous Phe508del Dose: 400 mg LUM-250 mg IVA	24 weeks ppFEV1 >40 2.8 (1.7 to 3.8; p <0.0001)
Jennings et al., 2017		11 months post 0.11 (-39 to 20; p 0.9)
Konstan et al., 2017	Homozygous Phe508del	Week 24 (TRAFFIC) 2.2 (1.3 to 3.0; p <0.0001) Week 72 (PROGRESS) 0.5 (-0.4 to 1.5; p 0.2806) Week 96 (PROGRESS) 0.5 (-0.7 to 1.6; p 0.4231) *data from continued use of iva-lum, see study for data for placebo transition
Wainwright et al., 2015	Homozygous Phe508del Lum 400 mg-IVA	Day 15* 2.2% Week 8* 3% Week 16* 2.5% Week 24* 2%
Wainwright et al., 2015	Homozygous Phe508del	Day 15* 2.8%

	Lum 600 mg-IVA		
		Week 8* 3%	
		Week 16* 3.5%	
		Week 24* 2.6%	

*p value for all time points when compared to the placebo <0.025

Table B2
Lumacaftor-Ivacaftor: baseline ppFEV1 <40% change in ppFEV1 (CI)

Article	**Mutation** **Medication Dose**	**Time Frame** **Age: >18**	**Time Frame** **Age: >12**
Elborn et al., 2016	Homozygous Phe508del 600 mg LUM-250 mg IVA		24 weeks 3.7 (0.5 to 6.5; p 0.024)
Elborn et al., 2016	Homozygous Phe508del 400 mg LUM-250 mg IVA		24 weeks 3.3 (0.2 to 6.4; p 0.036)
Hubert et al., 2017	Homozygous Phe508del	1 month ppFEV1 <30% 4.61 (0.76 to 8.46; p 0.02) ppFEV1 31 to 40% 0.43 (-1.80 to 2.65; p 0.81) 3 months ppFEV1 <30% 5.64 (0.54 to 10.74) ppFEV1 31 to 40% 1.69 (-1.8 to 2.65)	

Taylor-Cousar et al., 2018	homozygous Phe508del	Day 15 -1.7 (-3.2 to -0.1) Week 4 -0.4 (-1.6 to 0.8) Week 8 0.4 (-1.2 to 1.6) Week 24 -0.4 (-1.9 to 1.1)

Appendix C

Table C1

Tezacaftor-Ivacaftor baseline ppFEV1 40-90% change in ppFEV1 (CI)

Articles	**Mutation**	**Time Frame** **Age: >12**	**Time Frame** **Age: >18**	**Time Frame** **Age: <18**
Donaldson et al., 2018	Homozygous Phe508del		28 days Placebo -0.14 (-2.0 to 2.0) 10 mg TEZ 1.3 (-1.0 to 3.25) 30 mg TEZ 2.9 (1.0 to 4.75) 100 mg TEZ 3.75 (2.0 to 2.0 to 6.0; p <0.05) *all doses provided with 150 mg IVA	
Donaldson et al., 2018	Phe508del with G551D	28 days 100 mg TEZ-150 IVA 4.6 (1.0 to 8.0; p <0.05) Placebo-IVA 150 1.4 (-5.0 to 8.0)		
Rowe et al., 2017	Heterozygous Phe508del	8 weeks 6.8 (5.7 to 7.8; p <0.001)	8 weeks 6.0 (4.9 to 7.0)	8 weeks 12.0 (9.3 to 14.8)
Taylor-Cousar et al., 2017	Homozygous Phe508del	24 weeks		

		3.4 (2.7 to 4.0; p <0.001)

Table C2

Tezacaftor-Ivacaftor baseline ppFEV1 <40 change in ppFEV1 (CI)

Articles	**Mutation**	**Time Frame** **Age: >12**
Rowe et al., 2017	Heterozygous Phe508del	8 weeks 4.4 (1.1 to 7.8)

Appendix D

Table D1

Triple therapy with baseline ppFEV1 40-90% change in ppFEV1 (CI)

Article	**Mutation** **Medication Dose**	**Time Frame** **Age: >12 years**	**Time Frame** **Age: >18 years old**	**Placebo**
Heijerman et al., 2019	Homozygous Phe508del	4 weeks 10.4 (8.6 to 12.2)		
Keating et al., 2018	heterozygous Phe508del Dose: VX-445 200mg+ TZ-IVA		4 weeks 13.8 (10.9 to 16.6; p <0.001)	
Keating et al., 2018	Homozygous Phe508del Dose: VX-445 200mg+ TZ-IVA		4 weeks 11.0 (7.9 to 14.0; p <0.001)	
Middleton et al., 2019	heterozygous Phe508del	4 weeks 13.6 (12.4 to 14.8; p <0.001) 24 weeks 13.9 (12.8 to 15.0; p <0.001)		4 weeks -0.2 (-1.3 to 1.0) 24 weeks -0.4 (-1.5 to 0.7)

Table D2

Triple therapy effect between age groups change in ppFEV1 (CI)

Article	**Mutation**	**Time Frame** **Age:12-18 years old**	**Time Frame** **Age: >18 years old**
Middleton et al., 2019	heterozygous Phe508del	4 weeks 13.8 (10 to 17.5)	4 weeks 13.6 (11.9 to 15.8)