Interactive Poster: Click each section of poster to navigate

Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Years of Age and Older With Cystic Fibrosis and at Least One *F508del* Allele: Interim Results From a Phase 3, Open-Label Extension Study (VX19-445-107)

Felix Ratjen, MD[1]; Hugo Escobar, MD[2]; Jonathan M. Gaffin, MD[3]; Susanna A. McColley, MD[4]; Erica Roesch, MD[5]; Fadel E. Ruiz, MD[6]; Claire E. Wainwright, MD, MBBS[7]; Neil Ahluwalia, MD[8]; Chenghao Chu, PhD[8]; Sabrina Noel, PhD[8]; Samuel M. Moskowitz, MD[8]; David Waltz, MD[8]; Tanya G. Weinstock, MD[8]; Jane Davies, MD, MBChB[9]; for the VX19-445-107 Study Group

[1]*The Hospital for Sick Children, Toronto, Ontario, Canada;* [2]*The Children's Mercy Hospital, Kansas City, MO;* [3]*Boston Children's Hospital, Boston, MA;* [4]*Ann & Robert H. Lurie Children's Hospital of Chicago and Northwestern University Feinberg School of Medicine, Chicago, IL;* [5]*Rainbow Babies and Children's Hospital, Cleveland, OH;* [6]*Texas Children's Hospital, Houston, TX;* [7]*Queensland Children's Hospital, University of Queensland, South Brisbane, Queensland, Australia;* [8]*Vertex Pharmaceuticals Incorporated, Boston, MA;* [9]*National Heart and Lung Institute, Imperial College London, National Institute for Health Research Imperial Biomedical Research Centre, and Royal Brompton and Harefield National Health Service Foundation Trust, London, United Kingdom*

Poster 562

BACKGROUND AND OBJECTIVES

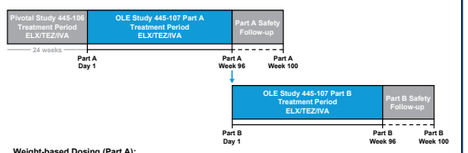
- Cystic fibrosis is a life-shortening genetic disease caused by mutations in the *CFTR* gene[1]
- Up to 90% of people with CF (pwCF) have ≥1 *F508del-CFTR* mutation, leading to decreased quantity and function of CFTR protein at the epithelial cell surface[1,2]
- Clinical symptoms of CF, including impaired growth, pancreatic insufficiency, and lung disease, generally appear during the first year of life.[3] Early diagnosis and treatment can improve clinical outcomes and extend life expectancy for pwCF[3,4]
- Recently, elexacaftor/tezacaftor/ivacaftor and ivacaftor (ELX/TEZ/IVA) was shown to be safe and efficacious in children 6 through 11 years of age with CF and ≥1 *F508del* allele in a 24-week pivotal study (Study 445-106)[5]
- Here, we report results from the Week 24 interim analysis (IA) of an ongoing open-label extension (Study 445-107) of Study 445-106

METHODS

Study Design and Endpoints

- Study 445-107 (NCT04183790) is a Phase 3, 2-part, multicenter, open-label extension (OLE) study designed to evaluate the long-term safety and efficacy of ELX/TEZ/IVA in children with CF who are 6 years of age and older and are either homozygous for *F508del-CFTR* (*F/F* genotype) or heterozygous for *F508del-CFTR* and a minimal function mutation (*F*/MF genotypes). Children who complete Part A will have the opportunity to enroll in Part B for an additional 96 weeks (**Figure 1**)
- **Primary Endpoint:** The primary endpoint is safety and tolerability, as assessed by adverse events (AEs), clinical laboratory values, electrocardiography, vital signs, pulse oximetry, and ophthalmologic examinations
- **Secondary Endpoints:** Secondary endpoints include absolute changes in percent predicted FEV_1 ($ppFEV_1$), sweat chloride concentration (SwCl), Cystic Fibrosis Questionnaire–Revised (CFQ–R) respiratory domain score, body mass index (BMI) and BMI *z*-score, and lung clearance index ($LCI_{2.5}$). The numbers of pulmonary exacerbations and CF-related hospitalizations were also assessed as secondary endpoints

Figure 1. Design of Study 445-107



Weight-based Dosing (Part A):
Weight <30 kg at OLE Day 1: 50% of adult dose of ELX/TEZ/IVA (ELX 100 mg once daily, TEZ 50 mg once daily, and IVA 75 mg every 12 hours)

Weight ≥30 kg at OLE Day 1 or at any 2 consecutive study visits during the treatment period: adult dose of ELX/TEZ/IVA (ELX 200 mg once daily, TEZ 100 mg once daily, and IVA 150 mg every 12 hours)

Inclusion Criteria (Part A):
- Completed study drug treatment in Study 445-106 or completed study visits up to the last scheduled visit in Study 445-106

ELX: elexacaftor; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; IVA: ivacaftor; OLE: open-label extension; TEZ: tezacaftor.

Week 24 Interim Analysis

- Data inclusion for the Week 24 IA was based on the date that the last participant reached Week 24 in Part A
  - For both efficacy and safety analyses, "baseline" refers to the pivotal study (Study 445-106) baseline
  - The safety analysis was based on all available data until the data cutoff date
  - The main efficacy analysis was based on all available data until the data cutoff date

Statistical Analysis

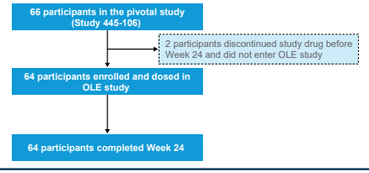
- Safety data were summarized using descriptive statistics
- A mixed-effects model for repeated measures was used to analyze changes from baseline in $ppFEV_1$, SwCl concentration, CFQ–R respiratory domain score, BMI and BMI *z*-score, and $LCI_{2.5}$. These analyses were similar to the analyses performed in the 24-week pivotal study. Analysis of the number of pulmonary exacerbations and CF-related hospitalizations were based on summary statistics

RESULTS

Participant Demographics and Clinical Characteristics

- A total of 64 children entered the OLE study from the 24-week pivotal study and received ≥1 dose of ELX/TEZ/IVA in the OLE study (**Figure 2**). Participant demographics and clinical characteristics at baseline are shown in **Table 1**

Figure 2. Participant Disposition



OLE: open-label extension.

Table 1. Baseline Demographics and Clinical Characteristics

	ELX/TEZ/IVA N = 64
Sex, n (%)	
Male	25 (39.1)
Female	39 (60.9)
Age at baseline[a], mean (SD), y	9.3 (1.8)
Baseline[a] weight <30 kg, n (%)	35 (54.7)
Genotype groups, n (%)	
F/F	28 (43.8)
F/MF	36 (56.3)
Baseline[a] $ppFEV_1$, mean (SD), percentage points	88.3 (17.6)
Baseline[a] SwCl concentration, mean (SD), mmol/L	102.2 (9.2)
Baseline[a] CFQ–R RD score, mean (SD), points	79.8 (15.2)
Baseline[a] BMI, mean (SD), kg/m^2	16.32 (1.66)
Baseline[a] BMI *z*-score, mean (SD)	–0.19 (0.73)
Baseline[a] $LCI_{2.5}$, mean (SD)	9.87 (2.68)

[a] Baseline is defined as the pivotal study (Study 445-106) baseline.
BMI: body mass index; CFQ–R: Cystic Fibrosis Questionnaire–Revised; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; $LCI_{2.5}$: lung clearance index (lung volume turnover required to reach 2.5% of starting N_2 concentration); RD: respiratory domain; SD: standard deviation; SwCl: sweat chloride.

Week 24 IA Safety Results

- Overall, 51 children (79.7%) had AEs in the OLE study through the Week 24 IA, which for all were either mild (51.6%) or moderate (28.1%) in severity (**Table 2**)
- The most common AEs (≥10%) were upper respiratory tract infection (14.1%), headache (10.9%), and vomiting (10.9%) (**Table 3**)
- Two children (3.1%) had serious AEs (exposure-adjusted event rate, 3.83 per 100 participant-years)
  - One child had a serious AE of idiopathic intracranial hypertension that led to study drug interruption. Study drug was resumed after symptoms improved
  - One child had a serious AE of anaphylactic reaction due to accidental peanut exposure that resolved on the same day
- Three children (4.7%) had alanine aminotransferase and/or aspartate aminotransferase (ALT/AST) >3× upper limit of normal (ULN), one of whom had ALT/AST >5× ULN. No children had ALT/AST >3× ULN with bilirubin >2× ULN. The exposure-adjusted event rate for AEs of elevated transaminase levels was 17.23 per 100 participant-years compared with 31.84 per 100 participant-years in the pivotal study
- The exposure-adjusted event rate for rash events was 9.57 per 100 participant-years compared with 60.79 per 100 participant-years in the pivotal study
  - Rash events is a group term that includes multiple preferred terms
- There were no notable safety findings in other clinical or laboratory assessments
- There were no discontinuations through the Week 24 IA

Table 2. Summary of Adverse Events

	Study 445-106 ELX/TEZ/IVA N = 66 Mean Exposure = 23.8 Weeks		Study 445-107 Week 24 IA ELX/TEZ/IVA N = 64 Mean Exposure = 39.2 Weeks	
	Patients (%)	Events/100 PY	Patients (%)	Events/100 PY
Patients with TEAE and total TEAE	65 (98.5)	987.04	51 (79.7)	315.83
AEs by maximum severity				
Mild	36 (54.5)	NA	33 (51.6)	NA
Moderate	28 (42.4)	NA	18 (28.1)	NA
Severe	1 (1.5)	NA	0 (0.0)	NA
Life threatening	0 (0.0)	NA	0 (0.0)	NA
AEs by strongest relationship				
Not related	16 (24.2)	NA	20 (31.3)	NA
Unlikely related	16 (24.2)	NA	18 (28.1)	NA
Possibly related	29 (43.9)	NA	13 (20.3)	NA
Related	4 (6.1)	NA	0 (0.0)	NA
SAEs	1 (1.5)	8.68	2 (3.1)	3.83
AEs leading to discontinuations	1 (1.5)	2.89	0 (0.0)	0
AEs leading to interruptions	1 (1.5)	8.68	2 (3.1)	3.83

AE: adverse event; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; NA: not applicable; PY: participant-years; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Table 3. Most Frequent Adverse Events (≥10%) in Pivotal Study (Study 445-106) or OLE Study (Study 445-107)

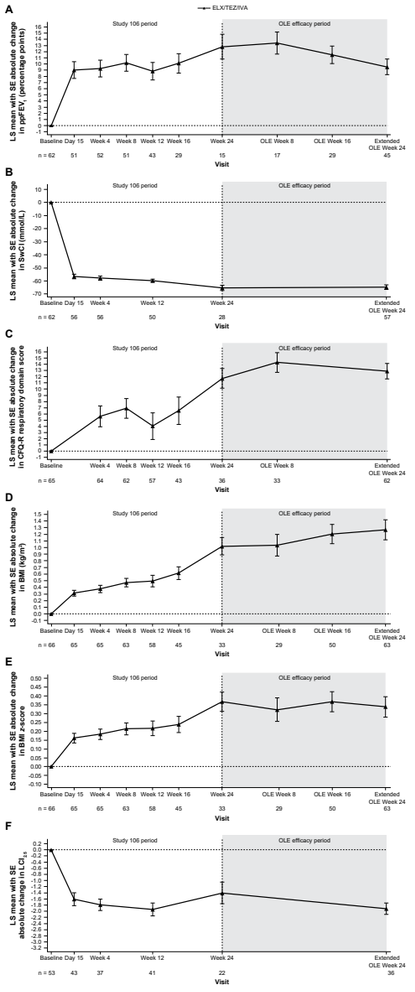
	Study 445-106 ELX/TEZ/IVA N = 66 Mean Exposure = 23.8 Weeks		Study 445-107 Week 24 IA ELX/TEZ/IVA N = 64 Mean Exposure = 39.2 Weeks	
	Patients (%)	Events/100 PY	Patients (%)	Events/100 PY
Patients with TEAE and total TEAE	65 (98.5)	987.04	51 (79.7)	315.83
Upper respiratory tract infection	11 (16.7)	40.52	9 (14.1)	17.23
Headache	16 (24.2)	55.00	7 (10.9)	19.14
Vomiting	7 (10.6)	28.95	7 (10.9)	17.23
Cough	28 (42.4)	121.57	6 (9.4)	13.40
Rhinorrhea	8 (12.1)	26.05	5 (7.8)	9.57
ALT increased	7 (10.6)	26.05	5 (7.8)	11.48
Pyrexia	14 (21.2)	55.00	4 (6.3)	11.48
Abdominal pain	8 (12.1)	26.05	4 (6.3)	7.66
Nasal congestion	10 (15.2)	40.52	3 (4.7)	5.74
Diarrhea	7 (10.6)	23.16	3 (4.7)	5.74
Oropharyngeal pain	12 (18.2)	40.52	1 (1.6)	1.91
Rash	8 (12.1)	28.95	1 (1.6)	1.91
Viral upper respiratory tract infection	8 (12.1)	23.16	1 (1.6)	3.83
Influenza	7 (10.6)	23.16	0 (0.0)	0

ALT: alanine aminotransferase; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; OLE: open-label extension; PY: participant-years; TEAE: treatment-emergent adverse event.

Week 24 IA Efficacy Results

- ELX/TEZ/IVA treatment resulted in improvements in $ppFEV_1$, sweat chloride concentration, CFQ–R respiratory domain score, BMI, BMI *z*-score, and $LCI_{2.5}$ from baseline at the Extended Week 24 Visit (**Figure 3** and **Table 4**), consistent with the pivotal study
  - Note that the Extended Week 24 Visit may include data from after the Week 24 Visit through the data cut if Week 24 Visit data were missing
- Overall, in the 24-week pivotal study and through Week 24 IA of the OLE study, 5 children (7.6%) had protocol-defined pulmonary exacerbations, with an observed annual rate of pulmonary exacerbations of 0.07. In comparison, the annual rate was 0.12 in Study 445-106. There were no CF-related hospitalizations in either the pivotal study or through Week 24 IA of the OLE study

Figure 3. Absolute Changes in ppFEV1, SwCl Concentration, CFQ–R Respiratory Domain Score, BMI, BMI *z*-score, and $LCI_{2.5}$ by Visit



BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire-revised; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; $LCI_{2.5}$: lung clearance index (lung volume turnover required to reach 2.5% of starting N_2 concentration); LS: least squares; OLE: open-label extension; SE: standard error; SwCl: sweat chloride.

Table 4. Absolute Changes from Baseline in Efficacy Results

Endpoints	Study 445-106 ELX/TEZ/IVA N = 66 Through Week 24	Study 445-107 Week 24 IA ELX/TEZ/IVA N = 64 At Extended Week 24
$ppFEV_1$, LS mean (SE), percentage points	10.2 (1.2)	9.5 (1.3)
Sweat chloride concentration, LS mean (SE), mmol/L	–60.9 (1.4)	–64.7 (1.7)
CFQ–R respiratory domain score, LS mean (SE), points	7.0 (1.1)	12.9 (1.2)
BMI, LS mean (SE), kg/m^2	1.02 (0.13)[a]	1.27 (0.15)
BMI *z*-score, LS mean (SE)	0.37 (0.05)[a]	0.34 (0.06)
$LCI_{2.5}$, LS mean (SE)	–1.71 (0.20)	–1.91 (0.18)

[a] At Week 24 of Study 445-106.
BMI: body mass index; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; $LCI_{2.5}$: lung clearance index (lung volume turnover required to reach 2.5% of starting N_2 concentration); LS: least squares; SE: standard error.

Subgroup Analysis of Secondary Endpoints

- An ad hoc subgroup analysis of absolute change in $ppFEV_1$ and sweat chloride concentration was conducted (**Table 5**)
- Consistent with the pivotal study, the decrease in LS mean sweat chloride concentration was greater in the *F/F* genotype group (–73.3 [SE, 2.0]) compared with the *F*/MF group (–58.8 [SE, 2.6]) from baseline at Extended Week 24 of the OLE study

Table 5. Subgroup Analysis of Absolute Change in $ppFEV_1$ and Sweat Chloride Concentration by Genotype

	$ppFEV_1$		SwCl	
	F/F	*F*/MF	*F/F*	*F*/MF
Pivotal study (Study 445-106)	**N = 29**	**N = 37**	**N = 29**	**N = 37**
Baseline, mean (SD)	87.3 (18.3)	89.8 (17.5)	99.3 (10.8)	104.4 (7.2)
Absolute change through Week 24, LS mean (SE)	11.2 (2.0)	9.1 (1.4)	–70.4 (2.4)	–55.1 (1.9)
OLE study (Study 445-107)	**N = 28**	**N = 36**	**N = 28**	**N = 36**
Absolute change at Extended Week 24, LS mean (SE)	12.2 (2.1)	7.0 (1.4)	–73.3 (2.0)	–58.8 (2.6)

F/F: *F508del/F508del*; *F*/MF: *F508del*/minimal function mutation; OLE: open-label extension; $ppFEV_1$: percentage of predicted FEV_1; LS: least squares; SD: standard deviation; SE: standard error; SwCl: sweat chloride.

CONCLUSIONS

- **ELX/TEZ/IVA was generally safe and well tolerated. The Week 24 interim results of this OLE study are consistent with the previously established safety profile of ELX/TEZ/IVA in children 6 through 11 years of age**
  - **All AEs were mild or moderate in severity, the number of serious AEs was low, and there were no discontinuations due to AEs**
  - **No new safety concerns were identified**
- **The robust, clinically meaningful improvements in lung function, respiratory symptoms, systemic CFTR activity, and nutritional parameters observed in the pivotal study were maintained through Week 24 of the OLE study. This indicates that ELX/TEZ/IVA provides durable benefit in this younger patient population**

References

1. Elborn JS. *Lancet*. 2016;388:2519-31.
2. Cystic Fibrosis Foundation. Patient Registry Annual Data Report, 2019. https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2019-Patient-Registry-Annual-Data-Report.pdf. Accessed August 2021.
3. VanDevanter DR, et al. *J Cyst Fibrosis*. 2016;15:147-57.
4. Farrell PM, et al. *Pediatrics*. 2001;107:1-13.
5. Zemanick ET, et al. *Am J Respir Crit Care Med*. 2021;203(12):1522-1532.

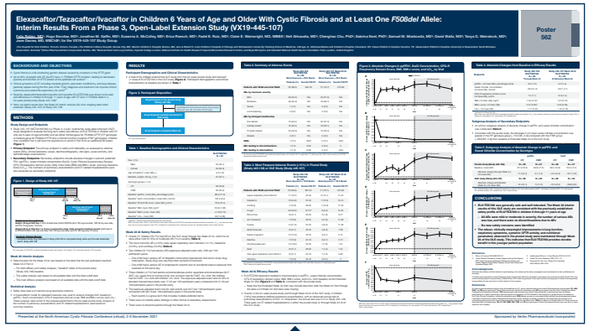
Acknowledgments

We thank the children and their families for participating in this study and the study investigators and coordinators for their contributions to the study.

The study was supported by Vertex Pharmaceuticals Incorporated. Editorial coordination and support was provided by Swati Thorat, PhD, and medical writing support was provided by Nathan Blow, PhD, under the guidance of the authors; both are employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options in the company.

Disclosures

All authors received editorial support from ArticulateScience LLC, which received funding from Vertex Pharmaceuticals Incorporated. **FR**, **JMG**, **SAM**, and **ER** report grants from Vertex Pharmaceuticals outside the submitted work. **HE** reports grants from the Cystic Fibrosis Foundation Therapeutics Development Network. **FER** reports grants and honoraria from Vertex Pharmaceuticals, consulting fees from UpToDate, participation on a safety monitoring or advisory board for the testing of CFTR modulators, and serving on a global advisory committee for the Cystic Fibrosis Foundation, outside the submitted work. **CEW** reports income on a per patient basis derived from pharmaceutical studies conducted, honoraria from Vertex Pharmaceuticals (advisory board, steering committee, consulting, and travel fees), and serving on an international advisory board for Vertex Pharmaceuticals, outside the submitted work. **CEW** also serves as a Deputy Editor for *Thorax* and as an Associate Editor for *Respirology*. **NA**, **CC**, **SN**, **SMM**, **DW**, **TGW**, and **JD** are employees of Vertex Pharmaceuticals and may own stock or stock options in the company.

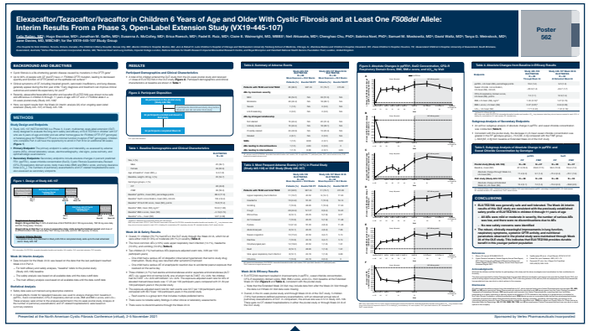


Click to return to main poster

BACKGROUND AND OBJECTIVES

- Cystic fibrosis is a life-shortening genetic disease caused by mutations in the *CFTR* gene[1]
- Up to 90% of people with CF (pwCF) have ≥1 *F508del-CFTR* mutation, leading to decreased quantity and function of CFTR protein at the epithelial cell surface[1,2]
- Clinical symptoms of CF, including impaired growth, pancreatic insufficiency, and lung disease, generally appear during the first year of life.[3] Early diagnosis and treatment can improve clinical outcomes and extend life expectancy for pwCF[3,4]
- Recently, elexacaftor/tezacaftor/ivacaftor and ivacaftor (ELX/TEZ/IVA) was shown to be safe and efficacious in children 6 through 11 years of age with CF and ≥1 *F508del* allele in a 24-week pivotal study (Study 445-106)[5]
- Here, we report results from the Week 24 interim analysis (IA) of an ongoing open-label extension (Study 445-107) of Study 445-106

Presented at the North American Cystic Fibrosis Conference (virtual), 2-5 November 2021 Sponsored by Vertex Pharmaceuticals Incorporated

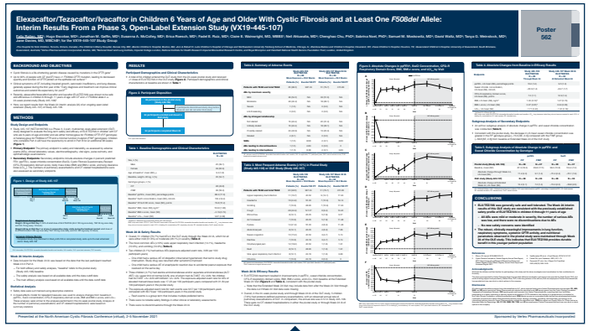


Click to return to main poster

METHODS (1 of 3)

Study Design and Endpoints

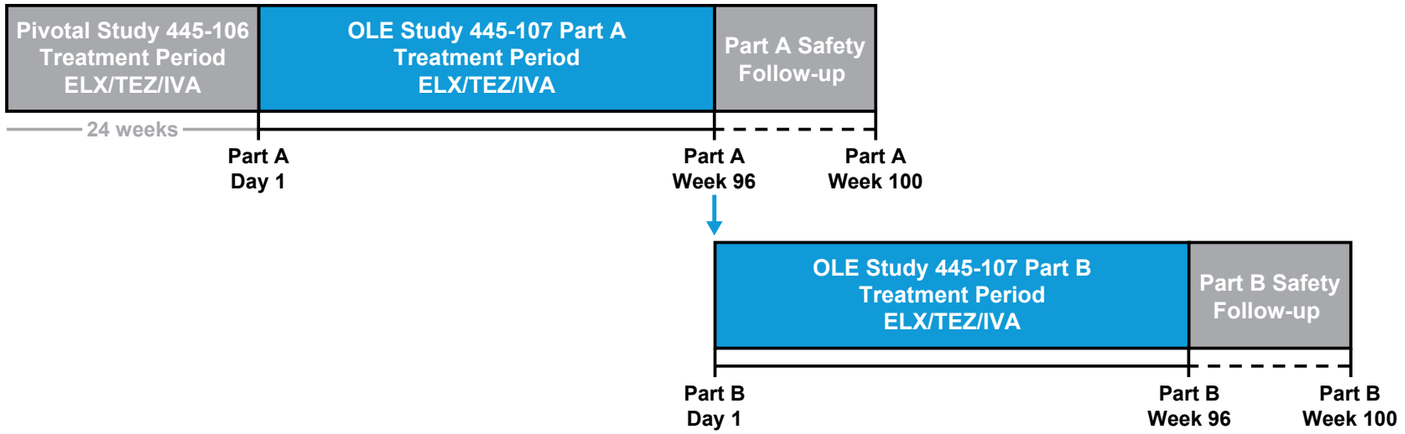
- Study 445-107 (NCT04183790) is a Phase 3, 2-part, multicenter, open-label extension (OLE) study designed to evaluate the long-term safety and efficacy of ELX/TEZ/IVA in children with CF who are 6 years of age and older and are either homozygous for *F508del-CFTR* (*F/F* genotype) or heterozygous for *F508del-CFTR* and a minimal function mutation (*F*/MF genotypes). Children who complete Part A will have the opportunity to enroll in Part B for an additional 96 weeks (**Figure 1**)
- **Primary Endpoint:** The primary endpoint is safety and tolerability, as assessed by adverse events (AEs), clinical laboratory values, electrocardiography, vital signs, pulse oximetry, and ophthalmologic examinations
- **Secondary Endpoints:** Secondary endpoints include absolute changes in percent predicted FEV_1 ($ppFEV_1$), sweat chloride concentration (SwCl), Cystic Fibrosis Questionnaire–Revised (CFQ–R) respiratory domain score, body mass index (BMI) and BMI *z*-score, and lung clearance index ($LCI_{2.5}$). The numbers of pulmonary exacerbations and CF-related hospitalizations were also assessed as secondary endpoints



Click to return to main poster

METHODS (2 of 3)

Figure 1. Design of Study 445-107



Weight-based Dosing (Part A):

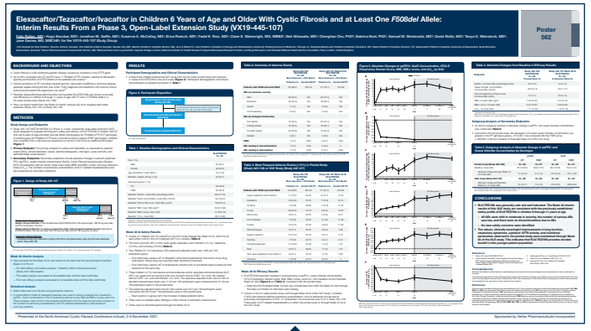
Weight <30 kg at OLE Day 1: 50% of adult dose of ELX/TEZ/IVA (ELX 100 mg once daily, TEZ 50 mg once daily, and IVA 75 mg every 12 hours)

Weight ≥30 kg at OLE Day 1 or at any 2 consecutive study visits during the treatment period: adult dose of ELX/TEZ/IVA (ELX 200 mg once daily, TEZ 100 mg once daily, and IVA 150 mg every 12 hours)

Inclusion Criteria (Part A):

- Completed study drug treatment in Study 445-106 or completed study visits up to the last scheduled visit in Study 445-106

ELX: elexacaftor; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; IVA: ivacaftor; OLE: open-label extension; TEZ: tezacaftor.



Click to return to main poster

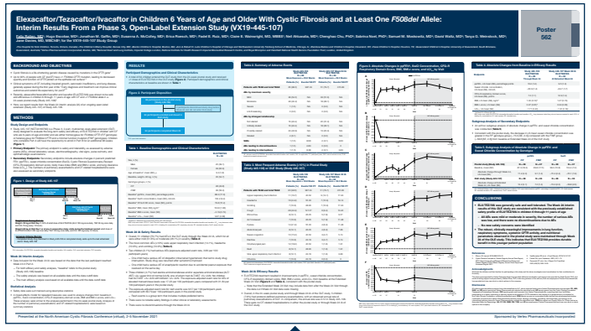
METHODS (3 of 3)

Week 24 Interim Analysis

- Data inclusion for the Week 24 IA was based on the date that the last participant reached Week 24 in Part A
  - For both efficacy and safety analyses, “baseline” refers to the pivotal study (Study 445-106) baseline
  - The safety analysis was based on all available data until the data cutoff date
  - The main efficacy analysis was based on all available data until the data cutoff date

Statistical Analysis

- Safety data were summarized using descriptive statistics
- A mixed-effects model for repeated measures was used to analyze changes from baseline in $ppFEV_1$, SwCl concentration, CFQ–R respiratory domain score, BMI and BMI *z*-score, and $LCI_{2.5}$. These analyses were similar to the analyses performed in the 24-week pivotal study. Analysis of the number of pulmonary exacerbations and CF-related hospitalizations were based on summary statistics



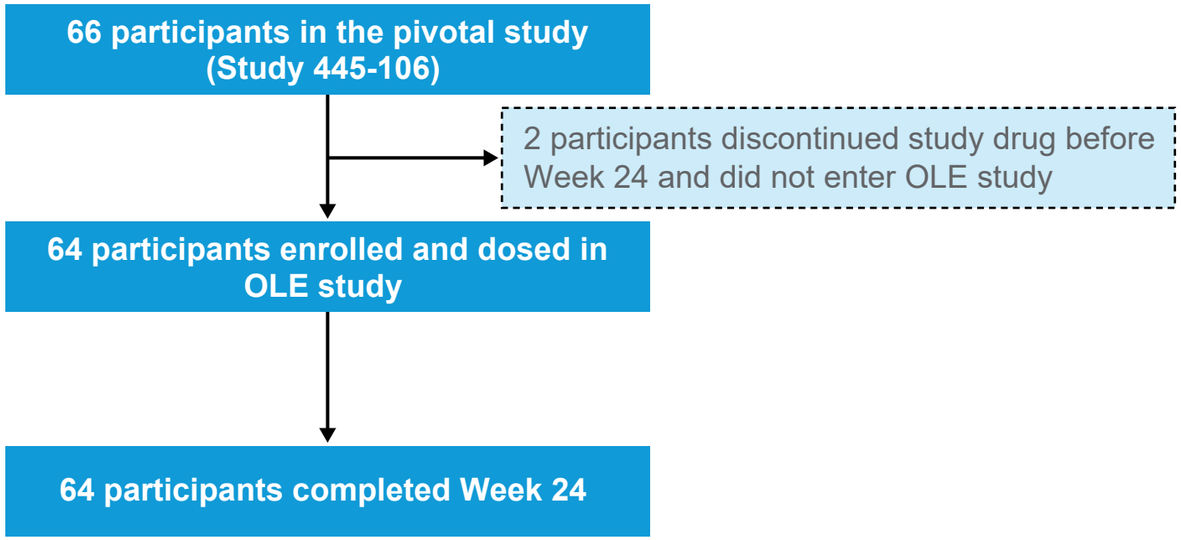
Click to return to main poster

RESULTS (1 of 14)

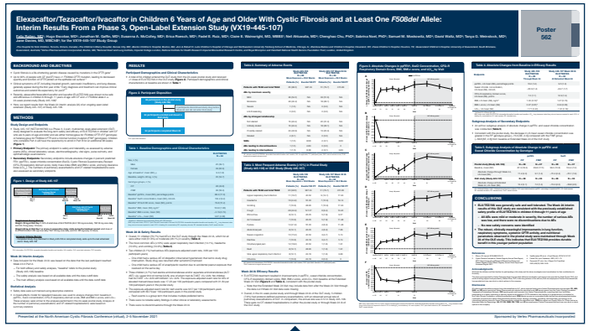
Participant Demographics and Clinical Characteristics

- A total of 64 children entered the OLE study from the 24-week pivotal study and received ≥1 dose of ELX/TEZ/IVA in the OLE study (**Figure 2**). Participant demographics and clinical characteristics at baseline are shown in **Table 1**

Figure 2. Participant Disposition



OLE: open-label extension.



Click to return to main poster

Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Years of Age and Older With Cystic Fibrosis and at Least One *F508del* Allele: Interim Results From a Phase 3, Open-Label Extension Study (VX19-445-107)

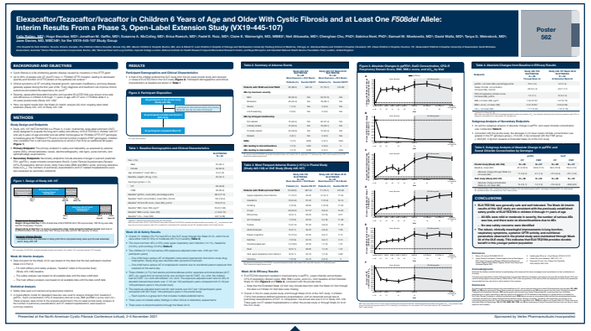
RESULTS (2 of 14)

Table 1. Baseline Demographics and Clinical Characteristics

	ELX/TEZ/IVA N = 64
Sex, n (%)	
Male	25 (39.1)
Female	39 (60.9)
Age at baseline[a], mean (SD), y	9.3 (1.8)
Baseline[a] weight <30 kg, n (%)	35 (54.7)
Genotype groups, n (%)	
F/F	28 (43.8)
F/MF	36 (56.3)
Baseline[a] $ppFEV_1$, mean (SD), percentage points	88.3 (17.6)
Baseline[a] SwCl concentration, mean (SD), mmol/L	102.2 (9.2)
Baseline[a] CFQ–R RD score, mean (SD), points	79.8 (15.2)
Baseline[a] BMI, mean (SD), kg/m^2	16.32 (1.66)
Baseline[a] BMI *z*-score, mean (SD)	–0.19 (0.73)
Baseline[a] $LCI_{2.5}$, mean (SD)	9.87 (2.68)

[a] Baseline is defined as the pivotal study (Study 445-106) baseline.
BMI: body mass index; CFQ–R: Cystic Fibrosis Questionnaire–Revised; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; $LCI_{2.5}$: lung clearance index (lung volume turnover required to reach 2.5% of starting N_2 concentration); RD: respiratory domain; SD: standard deviation; SwCl: sweat chloride.

Presented at the North American Cystic Fibrosis Conference (virtual), 2-5 November 2021 Sponsored by Vertex Pharmaceuticals Incorporated



Click to return to main poster

RESULTS (3 of 14)

Week 24 IA Safety Results

- Overall, 51 children (79.7%) had AEs in the OLE study through the Week 24 IA, which for all were either mild (51.6%) or moderate (28.1%) in severity (**Table 2**)
- The most common AEs (≥10%) were upper respiratory tract infection (14.1%), headache (10.9%), and vomiting (10.9%) (**Table 3**)
- Two children (3.1%) had serious AEs (exposure-adjusted event rate, 3.83 per 100 participant-years)
  - One child had a serious AE of idiopathic intracranial hypertension that led to study drug interruption. Study drug was resumed after symptoms improved
  - One child had a serious AE of anaphylactic reaction due to accidental peanut exposure that resolved on the same day
- Three children (4.7%) had alanine aminotransferase and/or aspartate aminotransferase (ALT/AST) >3× upper limit of normal (ULN), one of whom had ALT/AST >5× ULN. No children had ALT/AST >3× ULN with bilirubin >2× ULN. The exposure-adjusted event rate for AEs of elevated transaminase levels was 17.23 per 100 participant-years compared with 31.84 per 100 participant-years in the pivotal study
- The exposure-adjusted event rate for rash events was 9.57 per 100 participant-years compared with 60.79 per 100 participant-years in the pivotal study
  - Rash events is a group term that includes multiple preferred terms
- There were no notable safety findings in other clinical or laboratory assessments
- There were no discontinuations through the Week 24 IA

Click to return to main poster

Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Years of Age and Older With Cystic Fibrosis and at Least One *F508del* Allele: Interim Results From a Phase 3, Open-Label Extension Study (VX19-445-107)

Poster 562

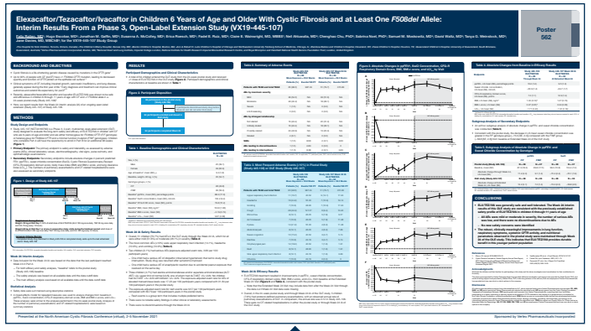
RESULTS (4 of 14)

Table 2. Summary of Adverse Events

	Study 445-106 ELX/TEZ/IVA N = 66 Mean Exposure = 23.8 Weeks		Study 445-107 Week 24 IA ELX/TEZ/IVA N = 64 Mean Exposure = 39.2 Weeks	
	Patients (%)	Events/100 PY	Patients (%)	Events/100 PY
Patients with TEAE and total TEAE	65 (98.5)	987.04	51 (79.7)	315.83
AEs by maximum severity				
Mild	36 (54.5)	NA	33 (51.6)	NA
Moderate	28 (42.4)	NA	18 (28.1)	NA
Severe	1 (1.5)	NA	0 (0.0)	NA
Life threatening	0 (0.0)	NA	0 (0.0)	NA
AEs by strongest relationship				
Not related	16 (24.2)	NA	20 (31.3)	NA
Unlikely related	16 (24.2)	NA	18 (28.1)	NA
Possibly related	29 (43.9)	NA	13 (20.3)	NA
Related	4 (6.1)	NA	0 (0.0)	NA
SAEs	1 (1.5)	8.68	2 (3.1)	3.83
AEs leading to discontinuations	1 (1.5)	2.89	0 (0.0)	0
AEs leading to interruptions	1 (1.5)	8.68	2 (3.1)	3.83

AE: adverse event; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; NA: not applicable; PY: participant-years; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Presented at the North American Cystic Fibrosis Conference (virtual), 2-5 November 2021 Sponsored by Vertex Pharmaceuticals Incorporated



Click to return to main poster

Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Years of Age and Older With Cystic Fibrosis and at Least One *F508del* Allele: Interim Results From a Phase 3, Open-Label Extension Study (VX19-445-107)

Poster 562

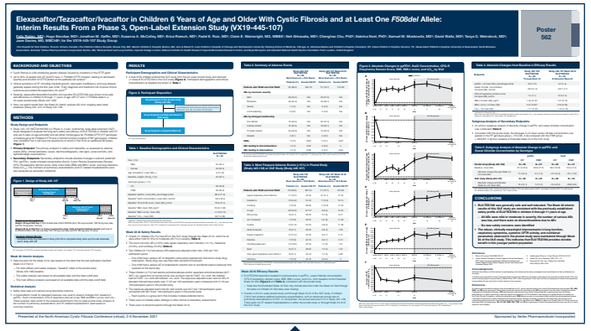
RESULTS (5 of 14)

Table 3. Most Frequent Adverse Events (≥10%) in Pivotal Study (Study 445-106) or OLE Study (Study 445-107)

	Study 445-106 ELX/TEZ/IVA N = 66 Mean Exposure = 23.8 Weeks		Study 445-107 Week 24 IA ELX/TEZ/IVA N = 64 Mean Exposure = 39.2 Weeks	
	Patients (%)	Events/100 PY	Patients (%)	Events/100 PY
Patients with TEAE and total TEAE	65 (98.5)	987.04	51 (79.7)	315.83
Upper respiratory tract infection	11 (16.7)	40.52	9 (14.1)	17.23
Headache	16 (24.2)	55.00	7 (10.9)	19.14
Vomiting	7 (10.6)	28.95	7 (10.9)	17.23
Cough	28 (42.4)	121.57	6 (9.4)	13.40
Rhinorrhea	8 (12.1)	26.05	5 (7.8)	9.57
ALT increased	7 (10.6)	26.05	5 (7.8)	11.48
Pyrexia	14 (21.2)	55.00	4 (6.3)	11.48
Abdominal pain	8 (12.1)	26.05	4 (6.3)	7.66
Nasal congestion	10 (15.2)	40.52	3 (4.7)	5.74
Diarrhea	7 (10.6)	23.16	3 (4.7)	5.74
Oropharyngeal pain	12 (18.2)	40.52	1 (1.6)	1.91
Rash	8 (12.1)	28.95	1 (1.6)	1.91
Viral upper respiratory tract infection	8 (12.1)	23.16	1 (1.6)	3.83
Influenza	7 (10.6)	23.16	0 (0.0)	0

ALT: alanine aminotransferase; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; OLE: open-label extension; PY: participant-years; TEAE: treatment-emergent adverse event.

Presented at the North American Cystic Fibrosis Conference (virtual), 2-5 November 2021 Sponsored by Vertex Pharmaceuticals Incorporated

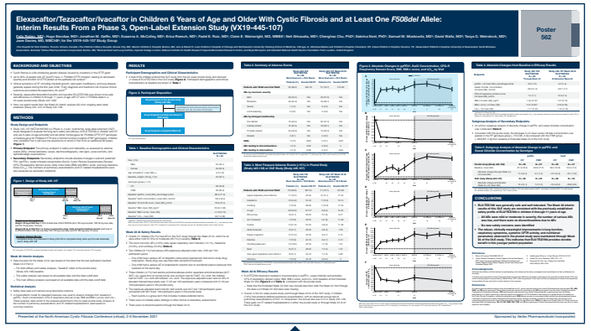


Click to return to main poster

RESULTS (6 of 14)

Week 24 IA Efficacy Results

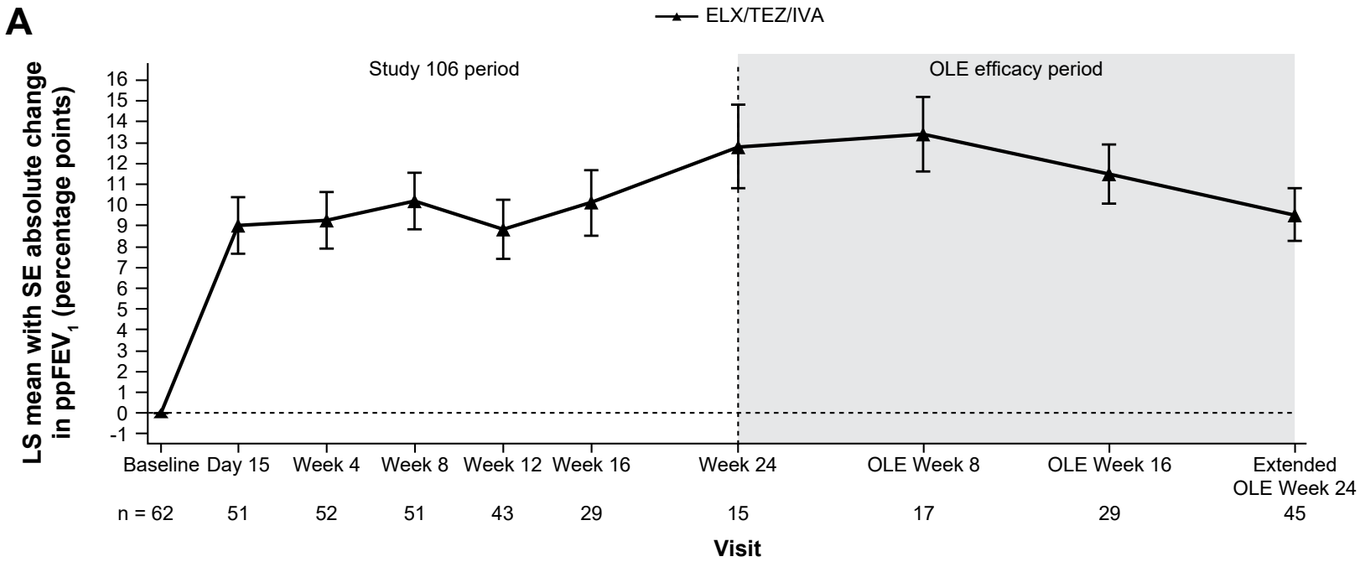
- ELX/TEZ/IVA treatment resulted in improvements in $ppFEV_1$, sweat chloride concentration, CFQ–R respiratory domain score, BMI, BMI *z*-score, and $LCI_{2.5}$ from baseline at the Extended Week 24 Visit (**Figure 3** and **Table 4**), consistent with the pivotal study
  - Note that the Extended Week 24 Visit may include data from after the Week 24 Visit through the data cut if Week 24 Visit data were missing
- Overall, in the 24-week pivotal study and through Week 24 IA of the OLE study, 5 children (7.6%) had protocol-defined pulmonary exacerbations, with an observed annual rate of pulmonary exacerbations of 0.07. In comparison, the annual rate was 0.12 in Study 445-106. There were no CF-related hospitalizations in either the pivotal study or through Week 24 IA of the OLE study



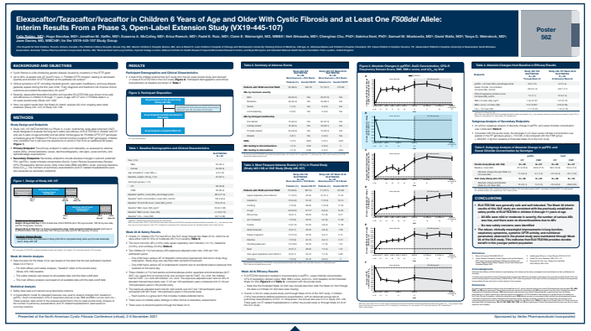
Click to return to main poster

RESULTS (7 of 14)

Figure 3. Absolute Changes in ppFEV1, SwCl Concentration, CFQ–R Respiratory Domain Score, BMI, BMI *z*-score, and $LCI_{2.5}$ by Visit



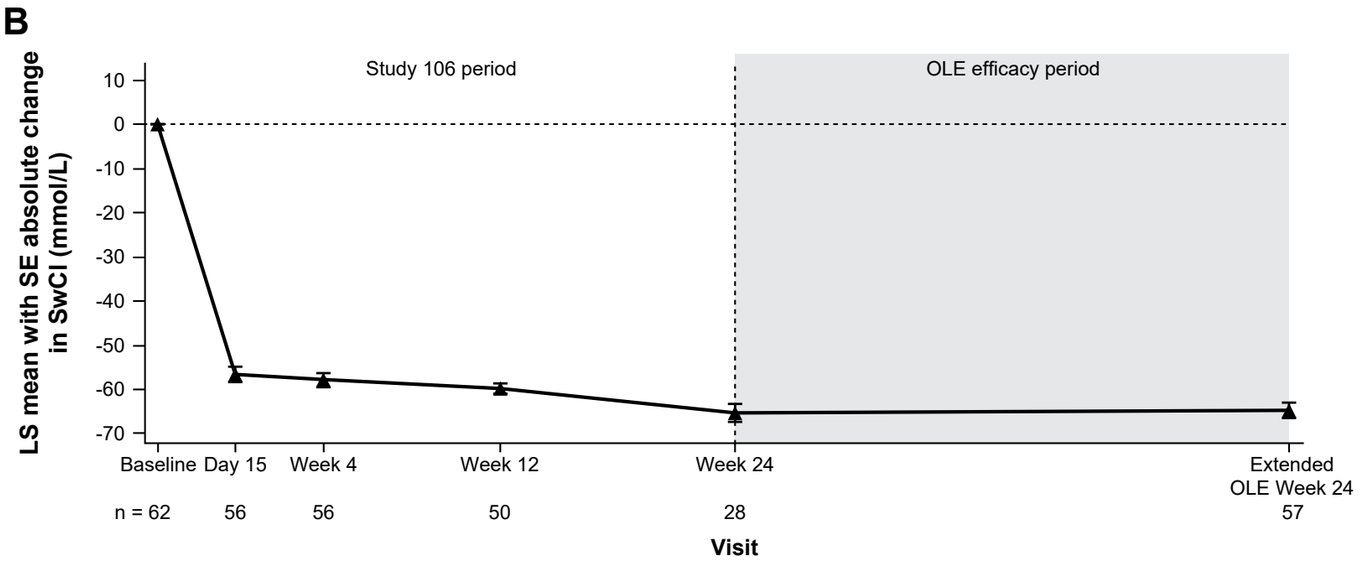
BMI: body mass index; CFQ–R: Cystic Fibrosis Questionnaire–revised; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; $LCI_{2.5}$: lung clearance index (lung volume turnover required to reach 2.5% of starting N_2 concentration); LS: least squares; OLE: open-label extension; SE: standard error; SwCl: sweat chloride.



Click to return to main poster

RESULTS (8 of 14)

Figure 3. Absolute Changes in ppFEV1, SwCl Concentration, CFQ–R Respiratory Domain Score, BMI, BMI *z*-score, and $LCI_{2.5}$ by Visit

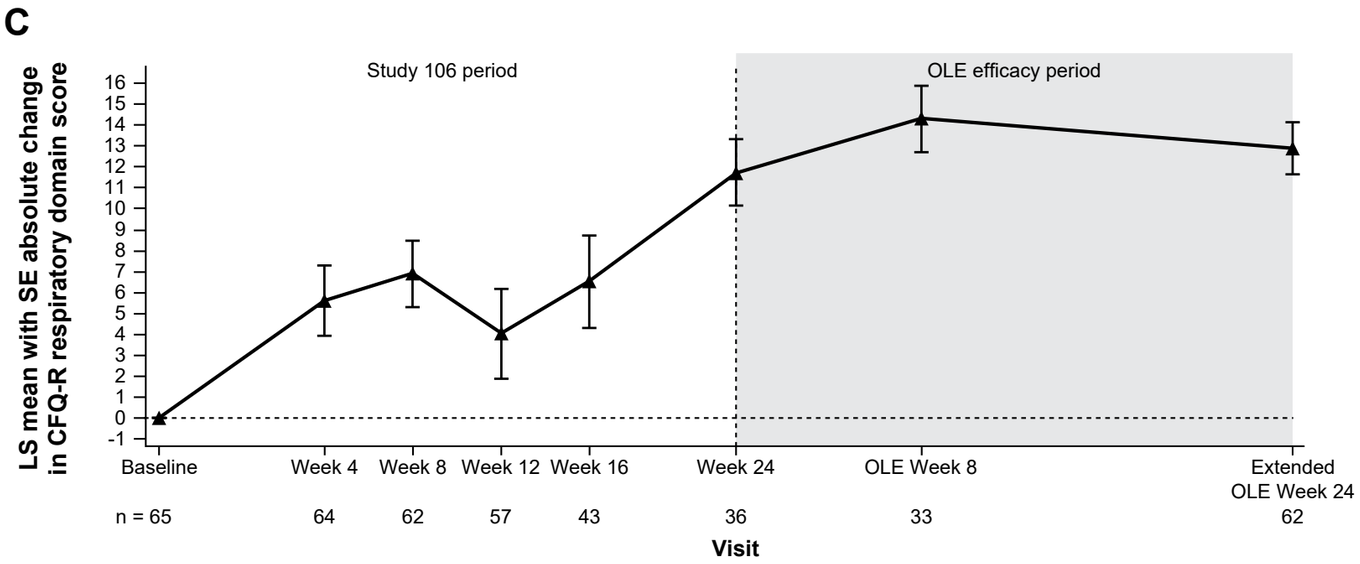


BMI: body mass index; CFQ–R: Cystic Fibrosis Questionnaire–revised; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; $LCI_{2.5}$: lung clearance index (lung volume turnover required to reach 2.5% of starting N_2 concentration); LS: least squares; OLE: open-label extension; SE: standard error; SwCl: sweat chloride.

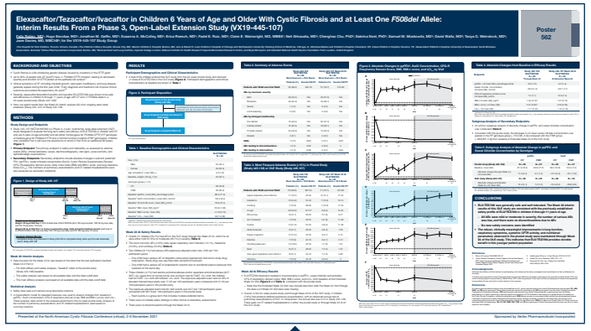
Click to return to main poster

RESULTS (9 of 14)

Figure 3. Absolute Changes in ppFEV1, SwCl Concentration, CFQ–R Respiratory Domain Score, BMI, BMI *z*-score, and $LCI_{2.5}$ by Visit



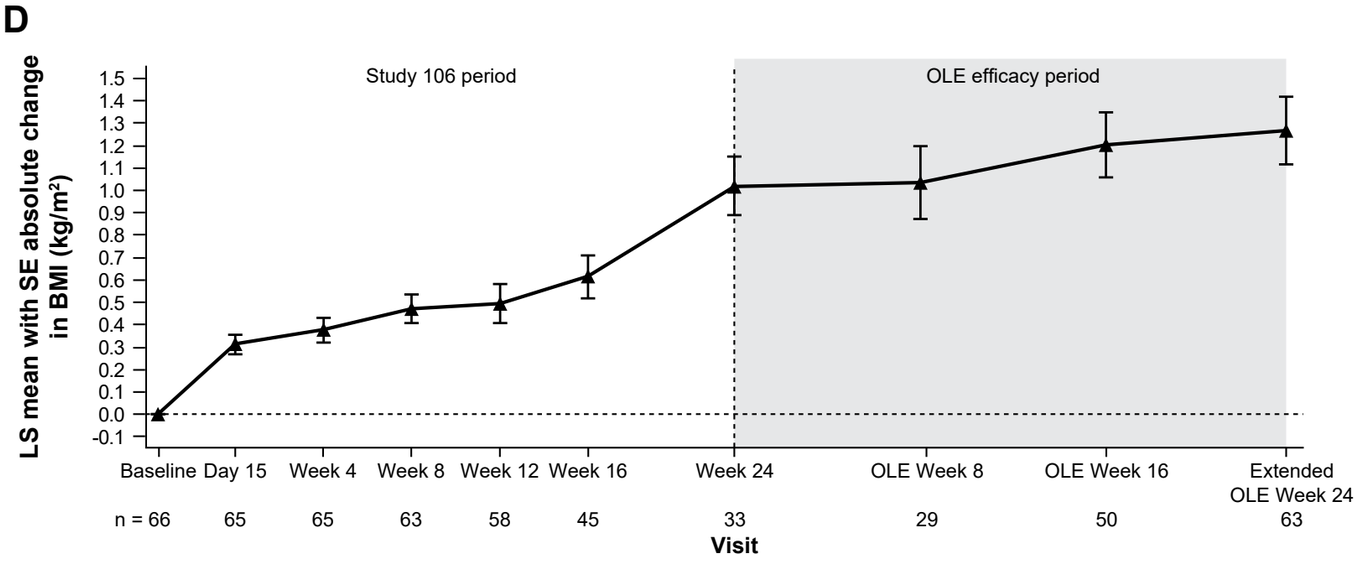
BMI: body mass index; CFQ–R: Cystic Fibrosis Questionnaire–revised; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; $LCI_{2.5}$: lung clearance index (lung volume turnover required to reach 2.5% of starting N_2 concentration); LS: least squares; OLE: open-label extension; SE: standard error; SwCl: sweat chloride.



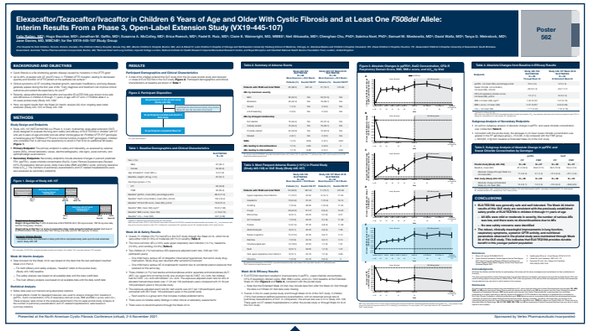
Click to return to main poster

RESULTS (10 of 14)

Figure 3. Absolute Changes in ppFEV1, SwCl Concentration, CFQ–R Respiratory Domain Score, BMI, BMI *z*-score, and $LCI_{2.5}$ by Visit



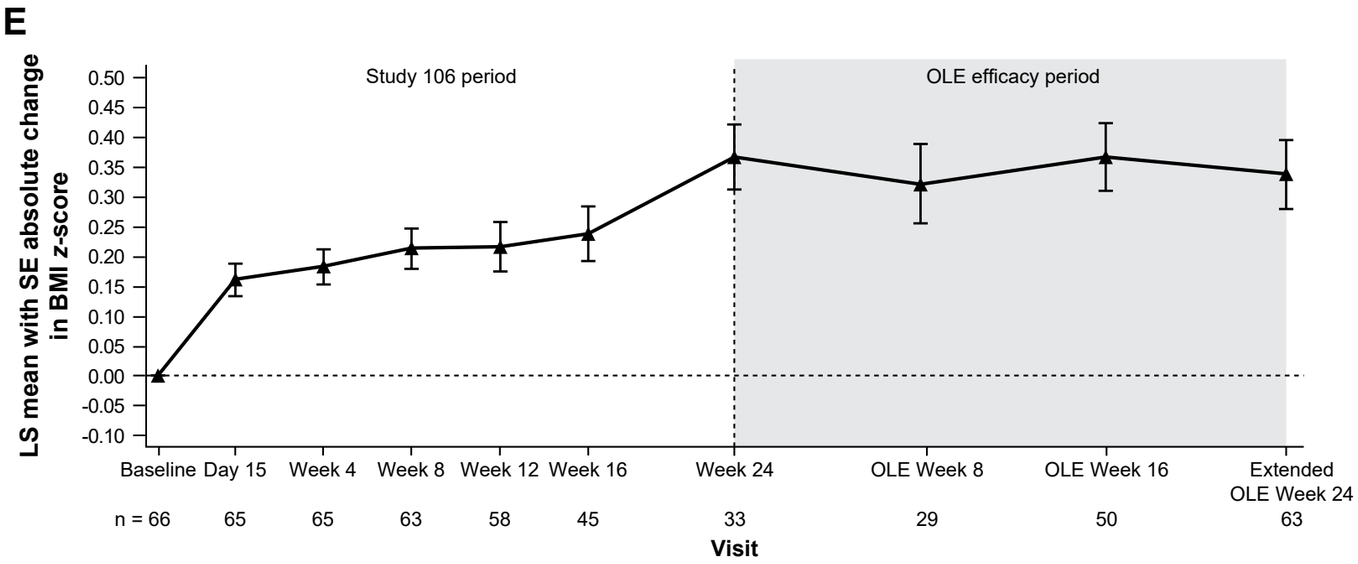
BMI: body mass index; CFQ–R: Cystic Fibrosis Questionnaire–revised; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; $LCI_{2.5}$: lung clearance index (lung volume turnover required to reach 2.5% of starting N_2 concentration); LS: least squares; OLE: open-label extension; SE: standard error; SwCl: sweat chloride.



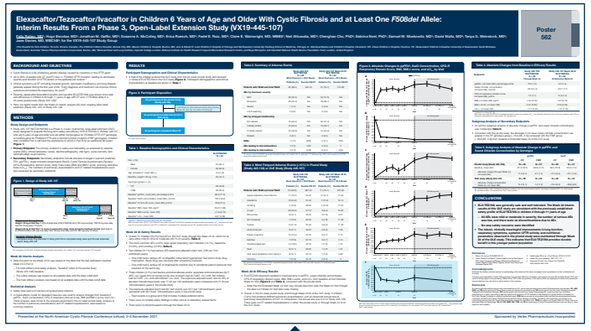
Click to return to main poster

RESULTS (11 of 14)

Figure 3. Absolute Changes in ppFEV1, SwCl Concentration, CFQ–R Respiratory Domain Score, BMI, BMI *z*-score, and $LCI_{2.5}$ by Visit



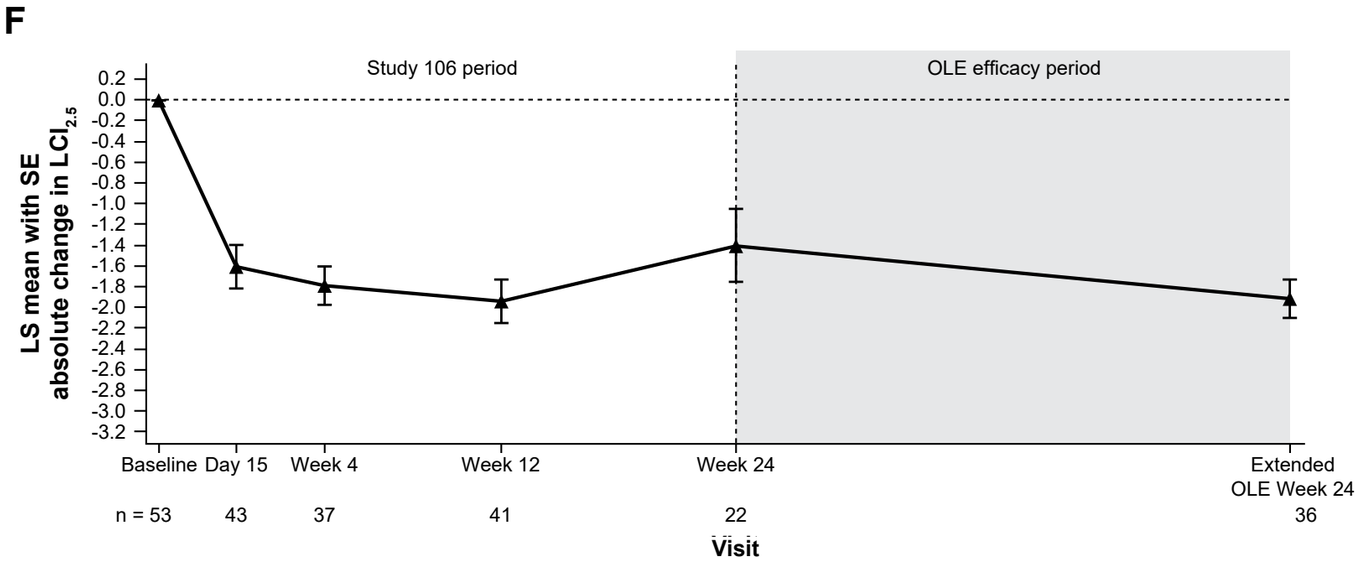
BMI: body mass index; CFQ–R: Cystic Fibrosis Questionnaire–revised; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; $LCI_{2.5}$: lung clearance index (lung volume turnover required to reach 2.5% of starting N_2 concentration); LS: least squares; OLE: open-label extension; SE: standard error; SwCl: sweat chloride.



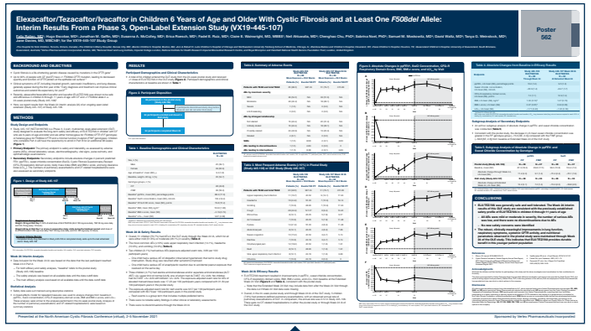
Click to return to main poster

RESULTS (12 of 14)

Figure 3. Absolute Changes in ppFEV1, SwCl Concentration, CFQ–R Respiratory Domain Score, BMI, BMI *z*-score, and $LCI_{2.5}$ by Visit



BMI: body mass index; CFQ–R: Cystic Fibrosis Questionnaire–revised; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; $LCI_{2.5}$: lung clearance index (lung volume turnover required to reach 2.5% of starting N_2 concentration); LS: least squares; OLE: open-label extension; SE: standard error; SwCl: sweat chloride.



Click to return to main poster

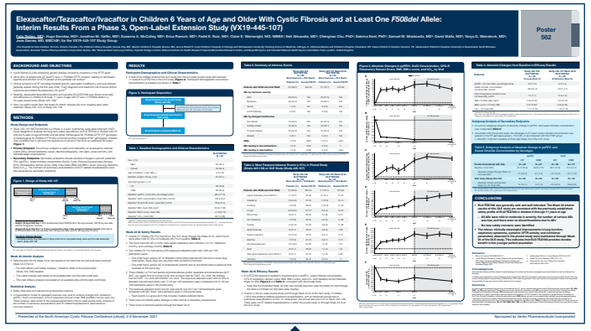
RESULTS (13 of 14)

Table 4. Absolute Changes from Baseline in Efficacy Results

Endpoints	Study 445-106 ELX/TEZ/IVA N = 66 Through Week 24	Study 445-107 Week 24 IA ELX/TEZ/IVA N = 64 At Extended Week 24
$ppFEV_1$, LS mean (SE), percentage points	10.2 (1.2)	9.5 (1.3)
Sweat chloride concentration, LS mean (SE), mmol/L	–60.9 (1.4)	–64.7 (1.7)
CFQ–R respiratory domain score, LS mean (SE), points	7.0 (1.1)	12.9 (1.2)
BMI, LS mean (SE), kg/m^2	1.02 (0.13)[a]	1.27 (0.15)
BMI *z*-score, LS mean (SE)	0.37 (0.05)[a]	0.34 (0.06)
$LCI_{2.5}$, LS mean (SE)	–1.71 (0.20)	–1.91 (0.18)

[a] At Week 24 of Study 445-106.

BMI: body mass index; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor and ivacaftor; $LCI_{2.5}$: lung clearance index (lung volume turnover required to reach 2.5% of starting N_2 concentration); LS: least squares; SE: standard error.



Click to return to main poster

RESULTS (14 of 14)

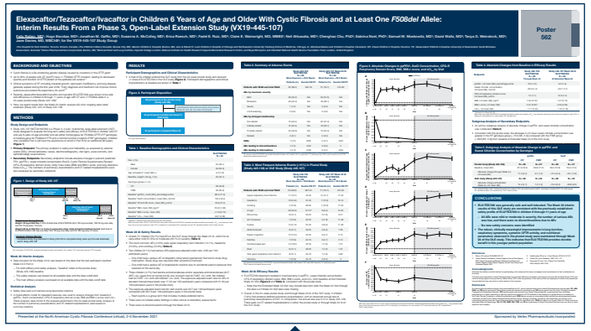
Subgroup Analysis of Secondary Endpoints

- An ad hoc subgroup analysis of absolute change in ppFEV$_1$ and sweat chloride concentration was conducted (**Table 5**)
- Consistent with the pivotal study, the decrease in LS mean sweat chloride concentration was greater in the *F/F* genotype group (–73.3 [SE, 2.0]) compared with the *F*/MF group (–58.8 [SE, 2.6]) from baseline at Extended Week 24 of the OLE study

Table 5. Subgroup Analysis of Absolute Change in ppFEV$_1$ and Sweat Chloride Concentration by Genotype

	ppFEV$_1$		SwCl	
	F/F	***F*/MF**	***F/F***	***F*/MF**
Pivotal study (Study 445-106)	**N = 29**	**N = 37**	**N = 29**	**N = 37**
Baseline, mean (SD)	87.3 (18.3)	89.8 (17.5)	99.3 (10.8)	104.4 (7.2)
Absolute change through Week 24, LS mean (SE)	11.2 (2.0)	9.1 (1.4)	–70.4 (2.4)	–55.1 (1.9)
OLE study (Study 445-107)	**N = 28**	**N = 36**	**N = 28**	**N = 36**
Absolute change at Extended Week 24, LS mean (SE)	12.2 (2.1)	7.0 (1.4)	–73.3 (2.0)	–58.8 (2.6)

F/F: *F508del/F508del*; *F*/MF: *F508del*/minimal function mutation; OLE: open-label extension; ppFEV$_1$: percentage of predicted FEV$_1$; LS: least squares; SD: standard deviation; SE: standard error; SwCl: sweat chloride.



Click to return to main poster

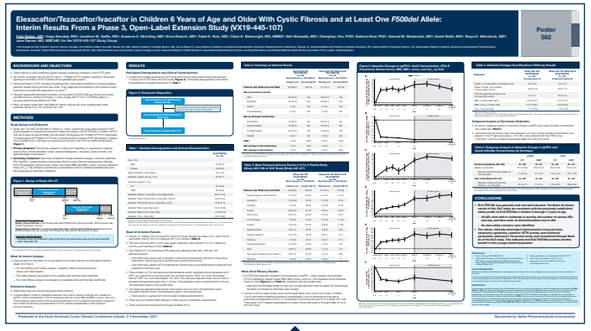
Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Years of Age and Older With Cystic Fibrosis and at Least One *F508del* Allele: Interim Results From a Phase 3, Open-Label Extension Study (VX19-445-107)

Poster 562

CONCLUSIONS

- **ELX/TEZ/IVA was generally safe and well tolerated. The Week 24 interim results of this OLE study are consistent with the previously established safety profile of ELX/TEZ/IVA in children 6 through 11 years of age**
  - **All AEs were mild or moderate in severity, the number of serious AEs was low, and there were no discontinuations due to AEs**
  - **No new safety concerns were identified**
- **The robust, clinically meaningful improvements in lung function, respiratory symptoms, systemic CFTR activity, and nutritional parameters observed in the pivotal study were maintained through Week 24 of the OLE study. This indicates that ELX/TEZ/IVA provides durable benefit in this younger patient population**

Presented at the North American Cystic Fibrosis Conference (virtual), 2-5 November 2021 Sponsored by Vertex Pharmaceuticals Incorporated



Click to return to main poster

BACKGROUND AND OBJECTIVES

METHODS

FIGURE 1

RESULTS

FIGURE 2

TABLE 1

TABLE 2

TABLE 3

FIGURE 3

TABLE 4

TABLE 5

CONCLUSIONS

REFERENCES, ACKNOWLEDGMENTS, AND DISCLOSURES

Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Years of Age and Older With Cystic Fibrosis and at Least One *F508del* Allele: Interim Results From a Phase 3, Open-Label Extension Study (VX19-445-107)

Poster 562

References

1. Elborn JS. *Lancet*. 2016;388:2519-31.
2. Cystic Fibrosis Foundation. Patient Registry Annual Data Report, 2019. https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2019-Patient-Registry-Annual-Data-Report.pdf. Accessed August 2021.
3. VanDevanter DR, et al. *J Cyst Fibrosis*. 2016;15:147-57.
4. Farrell PM, et al. *Pediatrics*. 2001;107:1-13.
5. Zemanick ET, et al. *Am J Respir Crit Care Med*. 2021;203(12):1522-1532.

Acknowledgments

We thank the children and their families for participating in this study and the study investigators and coordinators for their contributions to the study.

The study was supported by Vertex Pharmaceuticals Incorporated. Editorial coordination and support was provided by Swati Thorat, PhD, and medical writing support was provided by Nathan Blow, PhD, under the guidance of the authors; both are employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options in the company.

Disclosures

All authors received editorial support from ArticulateScience LLC, which received funding from Vertex Pharmaceuticals Incorporated. **FR**, **JMG**, **SAM**, and **ER** report grants from Vertex Pharmaceuticals outside the submitted work. **HE** reports grants from the Cystic Fibrosis Foundation Therapeutics Development Network. **FER** reports grants and honoraria from Vertex Pharmaceuticals, consulting fees from UpToDate, participation on a safety monitoring or advisory board for the testing of CFTR modulators, and serving on a global advisory committee for the Cystic Fibrosis Foundation, outside the submitted work. **CEW** reports income on a per patient basis derived from pharmaceutical studies conducted, honoraria from Vertex Pharmaceuticals (advisory board, steering committee, consulting, and travel fees), and serving on an international advisory board for Vertex Pharmaceuticals, outside the submitted work. **CEW** also serves as a Deputy Editor for *Thorax* and as an Associate Editor for *Respirology*. **NA**, **CC**, **SN**, **SMM**, **DW**, **TGW**, and **JD** are employees of Vertex Pharmaceuticals and may own stock or stock options in the company.