Online Data Supplement

Long-Term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in People With Cystic Fibrosis and at Least One *F508del* Allele: 144-Week Interim Results From a 192-Week Open-Label Extension Study

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Supplementary Methods

The trial was conducted in accordance with the Declaration of Helsinki, local applicable laws and regulations and current Good Clinical Practice Guidelines as described by the International Council for Harmonisation.

Study Inclusion Criteria

- Participant (or his or her legally appointed and authorised representative) signed and dated an informed consent form, and, when appropriate, an assent form
- Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines and other study procedures
- Did not withdraw consent from a parent study
- Meets ≥1 of the following criteria:
    a. Completed study drug treatment in a parent study
    b. Had a study drug interruption(s) in a parent study but completed study visits up to the last scheduled visit of the Treatment Period of a parent study
- Willing to remain on a stable cystic fibrosis (CF) treatment regimen through completion of study participation

Study Exclusion Criteria

- History of any comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the participant

- History of drug intolerance in a parent study that would pose an additional risk to the participant in the opinion of the investigator. (eg, participants with a history of allergy or hypersensitivity to the study drug.)
- Pregnant or nursing females. Females of childbearing potential must have had a negative pregnancy test at the Day 1 Visit before receiving the first dose of study drug
- Current participation in an investigational drug trial (other than a parent study). Participation in a noninterventional trial (including observational studies, registry studies and studies requiring blood collections without administration of study drug) and screening for another Vertex study was permitted

Study Design

Study VX17-445-105 is a Phase 3, multicentre, open-label, single-arm, extension study of the Phase 3 parent studies VX17-445-102 and VX17-445-103 that investigated elexacaftor (ELX) in combination with tezacaftor (TEZ) and ivacaftor (IVA) in participants with CF ≥12 years of age and either heterozygous for *F508del* and a minimal function mutation (*F/*MF) or homozygous for *F508del* (*F/F*). The total study duration will be approximately 196 weeks from first dose of ELX/TEZ/IVA in this study and includes a 192-week treatment period followed by a 4-week safety follow-up period.

During the trial, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic led to implementation of a global protocol addendum that enabled in-home assessments to mitigate the varying prohibitions on travel and the limitation of on-site research procedures based on governmental and institutional restrictions. Through this global protocol addendum, safety measures were implemented to provide participants the opportunity to continue

participating in this trial while minimising the risk of SARS-CoV-2 exposure through travel. Participant access to study drug therapy and collection of safety data were prioritised. These operational adjustments aligned with Health Authority guidance, ensuring the protection of participants, investigators and site personnel while maintaining compliance with Good Clinical Practice guidelines and minimising the impact of missed visits on study conduct. Implemented measures were based on country and local regulations, as well as site-level considerations, and included, as applicable, remote consent, shipment of the study drug, virtual study visits, in-home assessments (such as the Cystic Fibrosis Questionnaire–Revised) and remote monitoring.
The clinical trial protocol, SARS-CoV-2–related protocol addendum and informed consent forms were approved by independent ethics committees for each region or site, as required by local regulations.

Dosing

All participants receive ELX/TEZ/IVA at the same dose level as was evaluated in the parent studies (Study 445-102 and Study 445-103).

Adverse Events

Study assessments including laboratory tests, electrocardiograms, physical examinations and vital signs were assessed, and those deemed to have clinically significant worsening from baseline were documented as an adverse event (AE). When possible, a clinical diagnosis for the study assessment was provided, rather than the abnormal test result alone (eg, urinary tract infection, anaemia). In the absence of a diagnosis, the abnormal study assessment itself was listed as the AE (eg, bacteria in urine or decreased haemoglobin).

An abnormal study assessment was considered clinically significant if the participant has ≥1 of the following:

- Concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention
- A change in the dose of study drug or discontinuation from the study

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant was made by the investigator.

A laboratory value that is Grade 4 was automatically considered to be a serious AE. A Grade 4 laboratory value was a serious AE if the participant's clinical status indicates a life-threatening AE.

All AEs were collected from the time the informed consent form is signed until the participant completes study participation. All participants were queried, using nonleading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms were identified as one overall event or diagnosis. All AEs for enrolled participants were recorded in the case report form and source document. AEs for participants who were screened but not subsequently enrolled in the study were recorded only in the participant's source documents. The following data were documented for each AE:

- Description of the event
- Classification of 'serious' or 'non-serious'
- Date of first occurrence and date of resolution (if applicable)
- Severity

- Causal relationship of study drug(s)
- Action taken
- Outcome
- Concomitant medication or other treatment given

Statistical Analysis

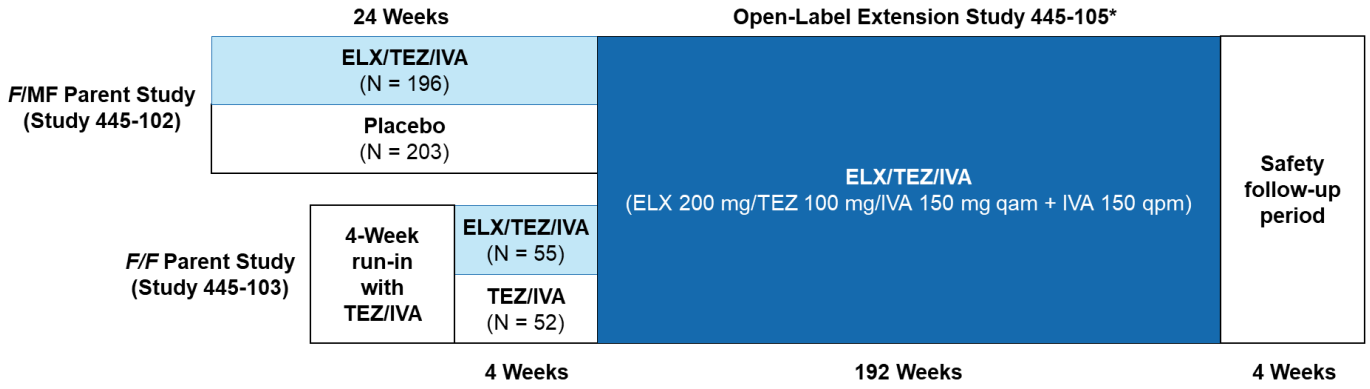
A total of 506 participants were dosed in this extension study. With the number of participants exposed to ELX/TEZ/IVA, adverse events by preferred term that occur with a frequency of >1% can be ruled out with 95% confidence when zero events are observed in that preferred term. Furthermore, with over 400 participants exposed to ELX/TEZ/IVA for at least 24 weeks, the half-width of the 95% confidence interval for estimating cumulative incidence of pulmonary exacerbations of CF is <6%, assuming an observed incidence of 30%. The baseline value for the long-term safety analysis, unless otherwise specified, was the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of ELX/TEZ/IVA in the parent study or extension study, as applicable. The baseline value for all efficacy analyses was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of the study drug in the parent study. Missing data was assumed to be missing at random, and no imputation of missing data was performed.

The annualised mean rate of change in per cent predicted forced expiratory volume at 1 second ($ppFEV_1$) was estimated for participants with *F/*MF and *F/F* genotypes separately, as well as for all participants together (genotype groups pooled), using a linear mixed-effects model with the cumulative efficacy period $ppFEV_1$ values as the dependent variable. Data obtained in the first 21 days from the first ELX/TEZ/IVA dose were excluded. In addition, participants with <3 non-

missing percentage of predicted FEV_1 measurements or non-missing $ppFEV_1$ measurements spanning <180 days were excluded as well. The model included time from first dose divided by 336 as fixed effects, age at screening of parent study (<18 vs ≥18 years of age) and sex (male vs female) as covariates, and a random intercept and time as the random effects. The mixed model was estimated using the restricted maximum likelihood method and assuming an unstructured covariance matrix for the random effect errors. The degrees of freedom in the denominator were estimated based on the method of Kenward-Roger (1).

Supplementary Figure

Figure S1. Study Design



Definition of abbreviations: ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; *F/F* = *F508del-F508del* genotype; *F*/MF = *F508del*-minimal function genotypes; TEZ/IVA = tezacaftor/ivacaftor; qam = once in the morning; qpm = once in the evening.

* In the extension study, participants received ELX/TEZ/IVA at the same dose level that was evaluated in the parent studies.

Supplementary Tables

Table S1. Additional Baseline Characteristics of the Participants*

	Sub-Group of Participants From Parent Study 445-102 (*F*/MF Genotypes)		**Sub-Group of Participants From Parent Study 445-103 (*F/F* Genotypes)**		**All Participants in Study 445-105**
	Placebo N = 203	**ELX/TEZ/IVA N = 196**	**TEZ/IVA N = 52**	**ELX/TEZ/IVA N = 55**	**ELX/TEZ/IVA N = 506**
Pseudomonas aeruginosa infection within 2 years prior to screening, n (%)					
Positive	142 (70.0)	147 (75.0)	31 (59.6)	39 (70.9)	359 (70.9)
Negative	61 (30.0)	49 (25.0)	21 (40.4)	16 (29.1)	147 (29.1)
Prior use of dornase alfa, n (%)†					
Yes	164 (80.8)	161 (82.1)	49 (94.2)	51 (92.7)	425 (84.0)
No	39 (19.2)	35 (17.9)	3 (5.8)	4 (7.3)	81 (16.0)
Prior use of azithromycin, n (%)†					
Yes	114 (56.2)	109 (55.6)	25 (48.1)	33 (60.0)	281 (55.5)
No	89 (43.8)	87 (44.4)	27 (51.9)	22 (40.0)	225 (44.5)
Prior use of inhaled antibiotic, n (%)†					
Yes	133 (65.5)	118 (60.2)	28 (53.8)	35 (63.6)	314 (62.1)
No	70 (34.5)	78 (39.8)	24 (46.2)	20 (36.4)	192 (37.9)
Prior use of any bronchodilator, n (%)†					
Yes	192 (94.6)	184 (93.9)	47 (90.4)	54 (98.2)	477 (94.3)
No	11 (5.4)	12 (6.1)	5 (9.6)	1 (1.8)	29 (5.7)
Prior use of any inhaled					

bronchodilator, n (%)[†]					
Yes	192 (94.6)	184 (93.9)	47 (90.4)	54 (98.2)	477 (94.3)
No	11 (5.4)	12 (6.1)	5 (9.6)	1 (1.8)	29 (5.7)
Prior use of any inhaled hypertonic saline, n (%)[†]					
Yes	130 (64.0)	147 (75.0)	43 (82.7)	38 (69.1)	358 (70.8)
No	73 (36.0)	49 (25.0)	9 (17.3)	17 (30.9)	148 (29.2)
BMI-for-age *z*-score, mean (SD) (participants aged ≤20 years)	−0.40 (0.98)	−0.37 (0.80)	−0.53 (0.91)	−0.37 (0.77)	−0.40 (0.88)

Definition of abbreviation: BMI = body mass index; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; TEZ/IVA = tezacaftor/ivacaftor.

* Baseline is defined as the most recent non-missing measurement before the first dose of study drug in the parent study treatment period. The open-label full analysis set is defined as all enrolled participants who received ≥1 dose of study drug in the open-label extension study.

[†] Includes medications started 56 days prior to the first dose of study drug in the treatment period.

Table S2. Adverse Events Occurring in >5% of Participants

	Study 445-102 Placebo N = 201		Study 445-102 ELX/TEZ/IVA N = 202		Study 445-105 ELX/TEZ/IVA N = 506	
Preferred Term	**n (%)**	**Events/100PY**	**n (%)**	**Events/100PY**	**n (%)**	**Events/100PY**
Participants with any AEs	193 (96.0)	1287.96	188 (93.1)	1096.01	500 (98.8)	586.55
Infective pulmonary exacerbation of cystic fibrosis	95 (47.3)	181.13	44 (21.8)	64.88	225 (44.5)	37.40
Cough	77 (38.3)	113.08	34 (16.8)	38.93	212 (41.9)	30.63
Headache	30 (14.9)	42.03	35 (17.3)	48.91	166 (32.8)	18.29
Oropharyngeal pain	25 (12.4)	26.02	20 (9.9)	26.95	146 (28.9)	16.85
Nasopharyngitis	26 (12.9)	34.03	22 (10.9)	29.95	135 (26.7)	17.04
Pyrexia	19 (9.5)	25.02	17 (8.4)	17.97	134 (26.5)	12.59
Sputum increased	39 (19.4)	47.03	40 (19.8)	46.91	120 (23.7)	12.09
Upper respiratory tract infection	22 (10.9)	26.02	24 (11.9)	29.95	111 (21.9)	11.65
Nasal congestion	15 (7.5)	18.01	19 (9.4)	20.96	106 (20.9)	10.08
Fatigue	20 (10.0)	22.02	9 (4.5)	8.98	104 (20.6)	11.21
COVID-19	0 (0)	0	0 (0)	0	99 (19.6)	7.70

	Study 445-102 Placebo N = 201		Study 445-102 ELX/TEZ/IVA N = 202		Study 445-105 ELX/TEZ/IVA N = 506	
Preferred Term	**n (%)**	**Events/100PY**	**n (%)**	**Events/100PY**	**n (%)**	**Events/100PY**
Nausea	14 (7.0)	17.01	16 (7.9)	15.97	84 (16.6)	7.77
Diarrhoea	14 (7.0)	23.02	26 (12.9)	31.94	80 (15.8)	6.64
Haemoptysis	28 (13.9)	42.03	11 (5.4)	11.98	78 (15.4)	12.03
Vaccination complication	0 (0)	0	0 (0)	0	78 (15.4)	9.52
Rhinorrhoea	6 (3.0)	7.01	17 (8.4)	18.97	69 (13.6)	5.95
Alanine aminotransferase increased	7 (3.5)	8.01	20 (9.9)	21.96	68 (13.4)	5.45
Constipation	12 (6.0)	12.01	6 (3.0)	5.99	68 (13.4)	5.64
Arthralgia	7 (3.5)	10.01	7 (3.5)	6.99	66 (13.0)	5.76
Sinusitis	8 (4.0)	8.01	11 (5.4)	14.97	66 (13.0)	7.02
Abdominal pain	12 (6.0)	20.01	20 (9.9)	23.96	65 (12.8)	5.76
Aspartate aminotransferase increased	4 (2.0)	4.00	19 (9.4)	20.96	65 (12.8)	4.82
Blood creatine phosphokinase increased	9 (4.5)	9.01	19 (9.4)	19.96	65 (12.8)	5.57
Dyspnoea	13 (6.5)	15.01	5 (2.5)	4.99	59 (11.7)	5.89
Vomiting	10 (5.0)	13.01	12 (5.9)	13.97	59 (11.7)	5.39
Sinus congestion	8 (4.0)	10.01	7 (3.5)	7.99	57 (11.3)	5.83
Influenza	3 (1.5)	3.00	14 (6.9)	15.97	53 (10.5)	4.07

	Study 445-102 Placebo N = 201		Study 445-102 ELX/TEZ/IVA N = 202		Study 445-105 ELX/TEZ/IVA N = 506	
Preferred Term	**n (%)**	**Events/100PY**	**n (%)**	**Events/100PY**	**n (%)**	**Events/100PY**
Rash	9 (4.5)	12.01	19 (9.4)	24.95	52 (10.3)	4.57
Productive cough	16 (8.0)	17.01	12 (5.9)	11.98	50 (9.9)	4.76
Rhinitis	11 (5.5)	14.01	15 (7.4)	17.97	49 (9.7)	6.70
Back pain	4 (2.0)	5.00	5 (2.5)	4.99	47 (9.3)	3.26
Acne	3 (1.5)	3.00	7 (3.5)	6.99	45 (8.9)	3.32
Abdominal pain upper	6 (3.0)	6.00	9 (4.5)	9.98	44 (8.7)	4.01
Bacterial test positive	10 (5.0)	13.01	5 (2.5)	4.99	42 (8.3)	3.82
Lower respiratory tract congestion	4 (2.0)	4.00	4 (2.0)	3.99	39 (7.7)	3.26
Urinary tract infection	0 (0)	0	4 (2.0)	3.99	37 (7.3)	2.88
Depression	2 (1.0)	2.00	1 (0.5)	1.00	36 (7.1)	2.69
Dizziness	5 (2.5)	7.01	7 (3.5)	6.99	36 (7.1)	2.82
Seasonal allergy	2 (1.0)	2.00	3 (1.5)	2.99	36 (7.1)	2.76
Pain	0 (0)	0	0 (0)	0	33 (6.5)	2.44
Anxiety	1 (0.5)	1.00	3 (1.5)	2.99	32 (6.3)	2.63
SARS-CoV-2 test positive	0 (0)	0	0 (0)	0	32 (6.3)	2.07
Pain in extremity	1 (0.5)	1.00	1 (0.5)	1.00	31 (6.1)	2.63

	Study 445-102 Placebo N = 201		Study 445-102 ELX/TEZ/IVA N = 202		Study 445-105 ELX/TEZ/IVA N = 506	
Preferred Term	**n (%)**	**Events/100PY**	**n (%)**	**Events/100PY**	**n (%)**	**Events/100PY**
Blood bilirubin increased	2 (1.0)	2.00	10 (5.0)	10.98	30 (5.9)	2.82
Hypoglycaemia	2 (1.0)	2.00	9 (4.5)	8.98	30 (5.9)	2.19
Pharyngitis	2 (1.0)	2.00	6 (3.0)	5.99	29 (5.7)	2.69
Respiration abnormal	4 (2.0)	4.00	9 (4.5)	9.98	29 (5.7)	2.57
Wheezing	2 (1.0)	2.00	6 (3.0)	6.99	29 (5.7)	2.63
Insomnia	1 (0.5)	1.00	3 (1.5)	2.99	28 (5.5)	2.07
Myalgia	5 (2.5)	5.00	5 (2.5)	4.99	28 (5.5)	2.07
Viral upper respiratory tract infection	4 (2.0)	4.00	9 (4.5)	11.98	28 (5.5)	2.44
Abdominal distension	3 (1.5)	4.00	5 (2.5)	6.99	27 (5.3)	2.19
Influenza like illness	2 (1.0)	2.00	0 (0)	0	27 (5.3)	2.00

Definition of abbreviation: AE = adverse event; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; PY = participant-years; SARS‑CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table S3. Summary of Most Common Adverse Events (>15% at Week 144) at Weeks 48, 96, and 144

	Study 445-105 Week 48 Interim Analysis ELX/TEZ/IVA N = 506		Study 445-105 Week 96 Interim Analysis ELX/TEZ/IVA N = 506		Study 445-105 Week 144 Interim Analysis ELX/TEZ/IVA N = 506	
	Mean Exposure = 37.2 Weeks		Mean Exposure = 105.7 Weeks		Mean Exposure = 151.1 Weeks	
	Participants	Events/100PY	Participants	Events/100PY	Participants	Events/100PY
Most common adverse events*, n (%)						
Infective pulmonary exacerbation of cystic fibrosis	127 (25.1)	49.60	191 (37.7)	38.69	225 (44.5)	37.40
Cough	118 (23.3)	44.26	183 (36.2)	32.87	212 (41.9)	30.63
Headache	66 (13.0)	24.93	124 (24.5)	17.73	166 (32.8)	18.29
Oropharyngeal pain	74 (14.6)	25.69	132 (26.1)	18.90	146 (28.9)	16.85
Nasopharyngitis	69 (13.6)	21.62	114 (22.5)	16.93	135 (26.7)	17.04
Pyrexia	44 (8.7)	12.46	95 (18.8)	11.55	134 (26.5)	12.59
Sputum increased	63 (12.5)	20.60	100 (19.8)	12.98	120 (23.7)	12.09
Upper respiratory tract infection	60 (11.9)	18.31	99 (19.6)	13.16	111 (21.9)	11.65
Nasal congestion	48 (9.5)	16.79	81 (16.0)	10.93	106 (20.9)	10.08
Fatigue	51 (10.1)	16.28	80 (15.8)	11.28	104 (20.6)	11.21
COVID -19	0 (0)	0	15 (3.0)	1.70	99 (19.6)	7.70

	Study 445-105 Week 48 Interim Analysis ELX/TEZ/IVA N = 506		Study 445-105 Week 96 Interim Analysis ELX/TEZ/IVA N = 506		Study 445-105 Week 144 Interim Analysis ELX/TEZ/IVA N = 506	
	Mean Exposure = 37.2 Weeks		Mean Exposure = 105.7 Weeks		Mean Exposure = 151.1 Weeks	
	Participants	Events/100PY	Participants	Events/100PY	Participants	Events/100PY
Nausea	32 (6.3)	8.65	62 (12.3)	7.25	84 (16.6)	7.77
Diarrhoea	38 (7.5)	10.43	65 (12.8)	7.07	80 (15.8)	6.64
Haemoptysis	36 (7.1)	15.77	58 (11.5)	11.10	78 (15.4)	12.03
Vaccination complication	0 (0)	0	16 (3.2)	1.88	78 (15.4)	9.52

* The most common adverse events that occurred in ≥15% of participants in the Week 144 interim analysis of Study 445-105; listing is according to the preferred term (Medical Dictionary for Regulatory Activities version 24.1).

Table S4. Liver Function Test Enzyme Elevations and Adverse Events of Elevated Transaminases

	Study 445-102 Placebo N = 201		**Study 445-102 ELX/TEZ/IVA N = 202**		**Study 445-105 ELX/TEZ/IVA N = 506**	
	Participants (%)	Events/100PY[§]	Participants (%)	Events/100PY[§]	Participants (%)	Events/100PY[§]
ALT or AST, n (%)*						
>3 × ULN	11 (5.5)	NA	16 (7.9)	NA	57 (11.3)	NA
>5 × ULN	3 (1.5)	NA	5 (2.5)	NA	32 (6.3)	NA
>8 × ULN	2 (1.0)	NA	3 (1.5)	NA	11 (2.2)	NA
ALT or AST and total bilirubin, n (%)*						
ALT or AST >3 × ULN and total bilirubin >2 × ULN	0	NA	2 (1.0)	NA	3 (0.6)[†]	NA
Elevated transaminase levels adverse event group term‡ — n (%)						
Any adverse event of elevated transaminase levels	8 (4.0)	13.01	22 (10.9)	42.92	82 (16.2)	10.43
Serious adverse events of elevated transaminase levels	1 (0.5)	1.00	0 (0)	0	6 (1.2)	0.69
Adverse events of elevated transaminase levels leading to treatment interruption	3 (1.5)	4.00	2 (1.0)	2.99	21 (4.2)	2.44
Adverse events of elevated transaminase levels leading to treatment discontinuation	0 (0)	0	0 (0)	0	6 (1.2)	0.75
Time-to-onset of first event, days						

Mean (SD)	61.8 (62.7)	--	78.4 (63.6)	--	384.6 (324.5)	--
Min, Max	1, 169	--	1, 176	--	1, 1097	--
Duration of events, days						
Mean (SD)	19.6 (14.6)	--	32.8 (34.0)	--	72.9 (116.3)	--
Min, Max	5, 52	--	4, 153	--	1, 837	--

Definition of abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; NA = not applicable; PY = participant-years; ULN = upper limit of normal.

* For the liver function test threshold analyses, each percentage is calculated as (n/N1)×100, where the numerator 'n' is the number of participants in the post-Triple-Combination-safety-baseline meeting the indicated threshold, and the denominator (N1) is the number of participants with ≥1 non-missing measurement during the open-label safety period. For 'ALT or AST', counts are based on the highest value of either test during the treatment-emergent period for each participant. A participant whose highest value is >5 × ULN is also counted as >3 × ULN. A participant whose highest value is >8 × ULN is also counted as >3 × ULN and >5 × ULN.

† Two participants (0.4%) in Study 445-105 had ALT or AST >3 × ULN with concurrent newly occurred bilirubin >2 × ULN. In a third participant, the ALT or AST >3 × ULN and bilirubin >2 × ULN elevations were not concurrent.

‡ Group term of 'elevated transaminase events' included multiple preferred terms.

§ Events per 100 participant-years was calculated by dividing the number of events by the total duration of the safety analysis period in 100 participant-years. 1 year = 48 weeks = 336 days.

Table S5. Summary of Rash Events*

	Study 445-102 Placebo N = 201		**Study 445-102 ELX/TEZ/IVA N = 202**		**Study 445-105 ELX/TEZ/IVA N = 506**	
	Participants (%)	Events/100PY	Participants (%)	Events/100PY	Participants (%)	Events/100PY
Any rash event, n (%)	13 (6.5)	19.01	22 (10.9)	29.95	82 (16.2)	7.08
Male, n/N1 (%)[†]	5/105 (4.8)	13.29	6/104 (5.8)	15.54	33/255 (12.9)	5.58
Female, n/N1 (%)[†]	8/96 (8.3)	25.40	16/98 (16.3)	45.16	49/251 (19.5)	8.68
Serious rash event, n (%)	2 (1.0)	2.00	3 (1.5)	2.99	2 (0.4)	0.13
Concomitant hormone therapy use,[‡] n/N1 (%)[†]	3/32 (9.4)	32.84	8/40 (20.0)	50.82	25/122 (20.5)	10.79
No concomitant hormone therapy use,[‡] n/N1 (%)[†]	5/64 (7.8)	21.86	8/58 (13.8)	41.33	24/129 (18.6)	6.64
Time-to-onset of first event, days						
Mean (SD)	51.2 (51.7)	--	36.7 (44.6)	--	241.2 (268.7)	--
Min, Max	1, 157	--	5, 157	--	1, 1120	--
Duration of events, days						
Mean (SD)	14.0 (14.4)	--	11.5 (17.0)	--	21.5 (41.9)	--
Min, Max	2, 61	--	1, 92	--	1, 254	--

Definition of abbreviations: ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; PY = participant-years.

* When summarising numbers and percentages of participants, a participant with multiple events within a category is counted only once in that category. Group term of 'rash events' includes terms of rash (eg, rash, rash erythematous, rash maculopapular, rash papular, skin exfoliation and urticaria).

† For analyses stratified by sex and concomitant hormone therapy use, each percentage is calculated as (n/N1)×100, where the numerator ‘n’ is the number of participants in the specified subgroup (ie, sex or concomitant hormone therapy use category) with rash events, and the denominator (N1) is the total number of participants in the specified subgroup.

‡ Hormone therapy included oestrogens and progestogens based on the standard drug groupings using the World Health Organization Drug Dictionary, version March 2021, format B3.

Table S6. Adverse Events of Blood Creatine Phosphokinase Increased

	Study 445-102 Placebo N = 201		**Study 445-102 ELX/TEZ/IVA N = 202**		**Study 445-105 ELX/TEZ/IVA N = 506**	
	Participants (%)	Events/100PY	Participants (%)	Events/100PY	Participants (%)	Events/100PY
Any adverse event of blood creatine phosphokinase increased, n (%)	9 (4.5)	9.01	19 (9.4)	19.96	65 (12.8)	5.57
Serious adverse events of blood creatine phosphokinase increased, n (%)	0 (0)	0	0 (0)	0	1 (0.2)	0.06

Definition of abbreviations: ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; PY = participant-years.

Table S7. Summary of Blood Pressure Data

	Study 445-102 Placebo N = 201			**Study 445-102 ELX/TEZ/IVA N = 202**			**Study 445-105 ELX/TEZ/IVA N = 506**		
	n	SBP — mean (SD) (mm Hg)	DBP — mean (SD) (mm Hg)	n	SBP — mean (SD) (mm Hg)	DBP — mean (SD) (mm Hg)	n	SBP — mean (SD) (mm Hg)	DBP — mean (SD) (mm Hg)
Parent study baseline	201	113.7 (12.1)	69.7 (9.4)	202	113.4 (11.7)	69.4 (9.7)	–	–	–
Change at Week 24	198	−0.1 (12.4)	0.3 (8.9)	198	3.1 (10.8)	1.9 (10.2)	–	–	–
Change at Extended Week 144	–	–	–	–	–	–	424	3.9 (12.5)	2.6 (9.0)

Definition of abbreviations: ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Baseline was the parent study baseline, defined as the most recent non-missing measurement before the first dose of study drug in the parent study treatment period.

Table S8. Adverse Events Related to Blood Pressure*

	Study 445-102 Placebo N = 201		**Study 445-102 ELX/TEZ/IVA N = 202**		**Study 445-105 ELX/TEZ/IVA N = 506**	
	Participants (%)	Events/100PY	Participants (%)	Events/100PY	Participants (%)	Events/100PY
Hypertension	1 (0.5)	1.00	0 (0)	0	8 (1.6)	0.56
Blood pressure increased	1 (0.5)	1.00	1 (0.5)	1.00	5 (1.0)	0.44
Diastolic hypertension	0 (0)	0	0 (0)	0	1 (0.2)	0.06
Essential hypertension	0 (0)	0	0 (0)	0	1 (0.2)	0.06
Blood pressure diastolic increased	0 (0)	0	0 (0)	0	1 (0.2)	0.06
Hypertensive urgency†	0 (0)	0	0 (0)	0	1 (0.2)	0.06

Definition of abbreviations: ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; PY = participant-years.

* All adverse events related to blood pressure were nonserious and did not require change in ELX/TEZ/IVA dosing; 7 participants required medication for elevated blood pressure.

† There was 1 serious AE of hypertensive urgency in a 52-year-old female with type 2 diabetes, chronic kidney disease and a history of hypertension. After approximately 2.5 years in Study 105, she was diagnosed with essential hypertension and cardiomyopathy that was assessed as not related to ELX/TEZ/IVA, and there was no change in study drug.

Table S9. Annualised Rate of Change in $ppFEV_1$*

	Participants With *F*/MF Genotypes	**Participants With *F/F* Genotype**	**All Participants**
Total number of participants	392	105	497
Estimate of slope (standard error) per 48 weeks, percentage points	0.08 (0.11)	0.03 (0.18)	0.07 (0.10)
95% confidence interval	(−0.14 to 0.30)	(−0.33 to 0.39)	(−0.12 to 0.26)

Definition of abbreviations: F/F = F508del-F508del genotype; *F*/MF = *F508del*-minimal function genotypes; $ppFEV_1$ = per cent predicted forced expiratory volume in 1 second.

* Based on the cumulative efficacy period in Study 445-102, Study 445-103 and Study 445-105, up to approximately 151 weeks of follow-up. Includes only post-baseline measurements beyond 21 days from treatment initiation and only participants having ≥3 non-missing $ppFEV_1$ records spanning ≥180 days

Table S10. Incidence of depression and depression-related adverse events in ELX/TEZ/IVA pivotal phase 3 trial (Study 445-102) and in the ELX/TEZ/IVA pooled clinical trial data*

Event	Exposure-adjusted event rate (per 100 PY)			
	Pivotal Study 445-102 Placebo N=201 100 PY	**Pivotal Study 445-102 ELX/TEZ/IVA N=202 100 PY**	**Pooled Data Placebo* N=1369 709 PY**	**Pooled Data ELX/TEZ/IVA** N=1711 3857 PY**
Any Depression AEs (SMQ)	5.0	2.0	3.24	3.32
Suicide attempt	0	0	0.14	0.08
Suicidal ideation	1.00	0	0.28	0.23
Completed suicide	0	0	0	0

Definition of abbreviations: AE = adverse event; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor and ivacaftor; PY = participant years.

*Placebo column includes data from participants who received placebo in the following 10 completed CFTR modulator studies: 445-102, 659-102, 809-103, 809-104, 661-106, 661-107, and 770-102 (studies in participants 12 years of age and older) and 445-116, 809-109, and 770-103 (studies in participants 6 through 11 years of age).

**ELX/TEZ/IVA column contains data from 14 completed studies in participants 6 years and older. Studies were: 445-102, 445-103, 445-105, 445-104, 445-110, 445-106 Part B, 445-121, 445-001 Part D and Part E, 445-113, 445-117, 445-126, 445-109, 445-115, and 445-116.

References

1. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics* 1997;53:983-997.

Data Sharing Statement

Vertex is committed to advancing medical science and improving participant health. This includes the responsible sharing of clinical trial data with qualified researchers. Proposals for the use of these data will be reviewed by a scientific board. Approvals are at the discretion of Vertex and will be dependent on the nature of the request, the merit of the research proposed and the intended use of the data. Please contact CTDS@vrtx.com if you would like to submit a proposal or need more information.