Real-World Analysis of Cystic Fibrosis Treatment with Elexacaftor/Tezacaftor/Ivacaftor (Trikafta®) and Associated Total Cost of Care and Healthcare Resource Utilization Among 16 Million Commercially Insured Members

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BACKGROUND

- Cystic Fibrosis (CF) is a chronic, progressive genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene resulting in a dysfunctional CFTR protein. Approximately 40,000 children and adults in the United States are living with CF.[1]
- CF is a multi-organ system disease with pulmonary and gastrointestinal manifestations being the most prevalent.[2] Pulmonary exacerbations contribute significant clinical burden and indicate acute worsening of pulmonary symptoms that accelerate declining lung function and decrease survival.[3,4]
- Unlike the traditional standard of care aimed at treating symptoms, CFTR modulators target the underlying cause of CF aiming to increase the amount of functional CFTR protein for responsive mutations.[5]
- The CFTR modulator elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) is a triple combination oral drug therapy that expands treatment eligibility to nearly 90% of the CF population based on age and genotype.[6] In clinical trials, ELX/TEZ/IVA demonstrated clinical efficacy that exceeds the benefits of previously available CFTR combination products.[7]
- Limited real-world data exist describing the effectiveness of ELX/TEZ/IVA and impact on direct healthcare costs among patients without previous CFTR therapy use.

OBJECTIVE

- To describe all-cause cost of care and all-cause healthcare resource utilization six months prior to and six months following ELX/TEZ/IVA initiation among CFTR treatment naïve, commercially insured members.

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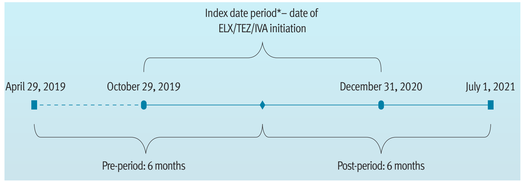
FIGURE 1

Study Design



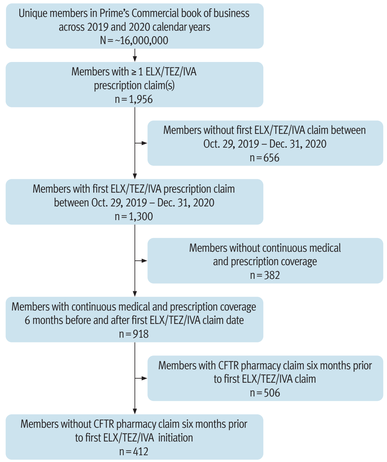
*Index date may occur at any time during the index date period. Earliest record of ELX/TEZ/IVA prescription claim was Oct. 29, 2019.
Abbreviations: ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor (Trikafta®).

METHODS

- This was a retrospective, observational cohort study using a six-month pre- and six-month post-study design.
- Study index date was defined as the first date of a prescription claim for ELX/TEZ/IVA between Oct. 29, 2019 and Dec. 31, 2020 **(Figure 1)**.
- Integrated medical and pharmacy claims data from April 29, 2019 to July 1, 2021 across Prime's commercial book of business were obtained for the study.
- Data included medical claims (date of service, diagnoses, procedures performed, place of service and claim paid amounts), pharmacy claims (fill dates, National Drug Code numbers and claim paid amounts), and eligibility information (patient demographics and enrollment history).
- Study inclusion was limited to members with first ELX/TEZ/IVA claim (index date) between Oct. 29, 2019 and Dec. 31, 2020, were continuously enrolled six months prior to (pre-period) and six months following (post-period) study index date and CFTR treatment naïve.
- CFTR treatment naïve was defined as no CFTR modulator drug claim (ivacaftor, tezacaftor/ivacaftor/ivacaftor, or lumacaftor/ivacaftor) during the six-month period prior to first ELX/TEZ/IVA claim.
- The primary outcome was six-month, all-cause direct total cost of care obtained from total paid amounts summed across medical and pharmacy benefits during the measure period. All-cause medical benefit and pharmacy benefit costs were obtained from paid, finalized claims by summing the total paid amounts (plan paid, member paid and any other third-party payment, if applicable) with network discounts applied. There are no ELX/TEZ/IVA pharmaceutical manufacturer rebates. Member cost discounts due to manufacturer coupons or patient assistance programs were not available and are not included.
- Other study outcomes included baseline demographics and clinical characteristics at the time of first ELX/TEZ/IVA pharmacy claim, CF treatment patterns, all-cause healthcare resource utilization (HRU) and the clinical outcome pulmonary exacerbation (PEx) events. All-cause HRU included inpatient stay and emergency department visits. Treatment patterns were characterized according to ELX/TEZ/IVA claim count and average six-month member cost.
- PEx event was operationalized based on Tesell et al. 2019[4] and defined as any one of the following events:
  - Any inpatient hospitalization with a medical diagnosis code in any position indicating CF PEx or respiratory infection
  - Any emergency department visit with a medical diagnosis code in any position indicating CF PEx or respiratory infection
  - Respiratory antibiotic (excluding oral macrolides and inhaled antibiotics) use identified from paid medical or pharmacy benefit claims
- A PEx event was considered new if a gap of seven or more days between events was observed between the end of a previous event and the start of a subsequent event.
- All study endpoints were calculated separately across separate six-month pre- and post-periods.
- Results were summarized using descriptive statistics and compared using nonparametric (signed-rank) paired test. An a priori alpha level of 0.05 was used to determine statistical significance.

FIGURE 2

Member Attrition



Cystic fibrosis transmembrane conductance regulator drug status was determined according to prescription drug claim history claims for Kalydeco® (ivacaftor), Symdeko® (tezacaftor/ivacaftor/ivacaftor), or Orkambi® (lumacaftor/ivacaftor) during the six-month pre-period.
Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor (Trikafta®).

TABLE 1

Demographics and Treatment Characteristics of 412 Members Newly Initiating Elexacaftor/Tezacaftor/Ivacaftor (Trikafta®)

	Utilizers N = 412	
Age at time of ELX/TEZ/IVA initiation, years		
Mean, SD	28.4	12.4
Median, 25th/75th percentile	26.5	18.4/35.0
Categorical		
< 12 years	3	0.7%
12 to < 18 years	91	22.1%
18 to < 35 years	218	52.9%
≥ 35 years	100	24.3%
Gender (n, %)		
Female	195	47.3%
Male	217	52.7%
ELX/TEZ/IVA claim count		
Total number of ELX/TEZ/IVA claims	2,708	---
Mean, SD	6.6	1.7
Median, 25th/75th percentile	7.0	6.0/7.0
Per utilizer per month	1.1	---
Number of ELX/TEZ/IVA claims (categorical) per member, (n, %)		
1	7	1.7%
2 to 5	63	15.3%
≥ 6	342	83.1%

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor (Trikafta®); n, number of utilizers; SD, standard deviation.

TABLE 2

Six-Month Pre-/Post-Pulmonary Exacerbation Events and All-Cause Healthcare Resource Utilization Among 412 Members Newly Initiating Elexacaftor/Tezacaftor/Ivacaftor (Trikafta®)

	Six months prior to ELX/TEZ/IVA initiation		Six months following ELX/TEZ/IVA initiation		% Change P Value
Pulmonary exacerbation events					
Total number of PEx events	675	---	319	---	- 53%
Mean, SD	1.6	1.4	0.8	0.9	< .001
Per utilizer per month	0.3	---	0.1	---	
Number of utilizers with PEx events, (n, %)					
0	104	25.2%	201	48.8%	
1	113	27.4%	134	14.7%	
≥2	195	47.3%	77	8.4%	
All-cause inpatient hospitalizations					
Total number of IP hospitalizations	199	---	58	---	- 71%
Mean, SD	0.5	1.1	0.1	0.6	< .001
Per utilizer per month	0.1	---	0.02	---	
Number of utilizers with IP hospitalizations, (n, %)					
0	300	72.8%	375	91.0%	
1	68	16.5%	25	6.1%	
≥2	44	10.7%	12	2.9%	
All-cause					
Total number of ED visits	126	---	70	---	- 44%
Mean, SD	0.3	1.0	0.2	0.6	0.01
Per utilizer per month	0.05	---	0.03	---	
Number of utilizers with ED visits, (n, %)					
0	341	82.8%	364	88.3%	
1	47	11.4%	36	8.7%	
≥2	24	5.8%	12	2.9%	

Percent (%) change calculated as the absolute percent change from the pre- to post-study period.
Abbreviations: ED, emergency department; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor (Trikafta®); IP, inpatient; n, number of utilizers; PEx, pulmonary exacerbation; SD, standard deviation.

TABLE 3

Six-Month Pre-/Post- All-Cause Direct Healthcare Costs Among 412 Members Newly Initiating Elexacaftor/Tezacaftor/Ivacaftor (Trikafta®)

	Six months prior to ELX/TEZ/IVA initiation		Six months following ELX/TEZ/IVA initiation		% Change P Value
All-cause total cost of care					
Mean, SD	$65,149	$71,631	$198,619	$71,030	+ 205%
Median, 25th/75th percentile	$46,039	$20,156/$80,881	$198,717	$172,095/$226,931	< .001
Per utilizer per month	$10,858	---	$33,103	---	
All-cause medical benefit cost					
Mean, SD	$31,345	$64,299	$11,260	$53,979	-64%
Median, 25th/75th percentile	$4,635	$1,069/$27,725	$1,985	$502/$6,092	< .001
Per utilizer per month	$5,224	---	$1,877	---	
All-cause pharmacy benefit cost					
Mean, SD	$33,804	$28,876	$187,359	$50,539	+ 454%
Median, 25th/75th percentile	$29,343	$11,407/$49,138	$192,392	$165,274/$217,604	< .001
Per utilizer per month	$5,634	---	$31,227	---	
Total ELX/TEZ/IVA cost					
Mean, SD	---	---	$156,977	$40,165	---
Median, 25th/75th percentile	---	---	$167,173	$144,839/$171,075	---
Per utilizer per month	---	---	$26,163	---	
All-cause inpatient hospitalization cost					
Mean, SD	$19,221	$55,675	$4,769	$42,814	-75%
Median, 25th/75th percentile	$0	$0/$2,130	$0	$0/$0	< .001
Per utilizer per month	$3,204	---	$795	---	
All-cause emergency department cost					
Mean, SD	$366	$1,389	$212	$1,080	-42%
Median, 25th/75th percentile	$0	$0/$0	$0	$0/$0	0.01
Per utilizer per month	$61	---	$35	---	

Percent (%) change calculated as the absolute percent change from the pre- to post-study period.
Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor (Trikafta®); n, number of utilizers; SD, standard deviation.

RESULTS

- Among 1,300 ELX/TEZ/IVA utilizers during the 14-month study index period, 412 (32.4%) met full study inclusion criteria; 382 members did not meet continuous enrollment criteria and 506 were excluded due to prior CFTR use **(Figure 2)**.
- A majority of utilizers were male (52.7%), and the average age was 28.4 years (standard deviation [SD] = 12.4) at time of ELX/TEZ/IVA initiation **(Table 1)**.
- As shown in **Table 1**, the average number of ELX/TEZ/IVA claims per utilizer was 6.6 (SD = 1.7) after six months.
- More than three-fourths (83.1%) of utilizers had six or more ELX/TEZ/IVA claims, 15.3% had two to five claims and 1.7% had one ELX/TEZ/IVA claim over six months.
- **Table 2** summarizes the real-world effectiveness of ELX/TEZ/IVA therapy. Compared to the six months prior to ELX/TEZ/IVA initiation:
  - Ninety-seven fewer utilizers experienced ≥ 1 pulmonary exacerbation event, 75 fewer utilizers experienced ≥ 1 hospitalization, and 23 fewer utilizers experienced ≥ 1 emergency department visit six months following therapy initiation. A significant reduction (53% absolute reduction, P < .001) in the number of pulmonary exacerbation events was observed six months following therapy initiation (pre-period: 1.6 average per utilizer [SD = 1.4] vs. post-period: 0.8 average per utilizer [SD = 0.9]).
  - A significant reduction (71% absolute reduction, P < .001) in the number of all-cause inpatient hospitalizations was observed six months following therapy initiation (pre-period: 0.5 average per utilizer [SD = 1.1] vs. post-period: 0.1 average per utilizer [SD = 0.6]).
  - A significant reduction (44% absolute reduction, P = .01) in the number of all-cause emergency department visits was observed six months following therapy initiation (pre-period: 0.3 average per utilizer [SD = 1.0] vs. post-period: 0.2 average per utilizer [SD = 0.6]).
- **Table 3** summarizes six-month, all-cause direct healthcare costs prior to and following ELX/TEZ/IVA initiation.
  - Per ELX/TEZ/IVA utilizer, the all-cause total cost of care was significantly higher (205% absolute increase, P < .001) following therapy initiation (post-period: $198,619 average per utilizer [SD = $71,030]) compared to the six months prior (pre-period: $65,149 aver-age per utilizer [SD = $71,631]).
  - All-cause medical benefit cost was significantly lower (64% absolute reduction, P < .001) following therapy initiation (post-period: $11,260 average per utilizer [SD = $53,979]) compared to the six months prior (pre-period: $31,345 average per utilizer [SD = $64,299]).
    - Significant reductions in all-cause inpatient hospitalization cost (75% absolute reduction; pre-period: $19,221 [SD = $55,675] vs. post-period: $4,769 [SD = $42,814]; P < .001) and all-cause emergency department cost (42% absolute reduction; pre-period: $366 [SD = $1,389] vs. post-period: $212 [SD = $1,080]; P = .01) were observed.
  - All-cause pharmacy benefit cost was significantly higher (454% absolute increase, P < .001) following therapy initiation (post-period: $187,359 average per utilizer [SD = $50,539]) compared to the six months prior (pre-period: $33,804 average per utilizer [SD = $28,876]).

LIMITATIONS

- This study was retrospective in nature and data were sourced from administrative healthcare claims. Claims data are subject to coding errors which could impact the final reporting of utilization and total paid amounts.
- Differences observed across the pre-/post-study periods may be attributed to factors other than ELX/TEZ/IVA therapy. The separate six-month observation windows were selected as a trade-off to mitigate the impact of extraneous factors while providing useful insight into short-term cost and clinical benefit immediately following ELX/TEZ/IVA initiation.
- Our definition of CFTR treatment naïve status is limited to six months of drug claims which may result in the misclassification of CFTR treatment status due to the potential for receiving CFTR therapy prior to the defined six-month observation window.
- Findings are limited to commercially insured members and may not be representative of members insured under government programs.

CONCLUSIONS

- This large cohort study found a statistically significant reduction in pulmonary exacerbation events, inpatient hospitalization, emergency department visits and medical costs in the six months following ELX/TEZ/IVA initiation.
- Our findings further describe a notable shift in costs across both the medical and pharmacy benefits. We observed a $25,593 average increase per utilizer per month in pharmacy benefit costs that were not offset by the $3,347 average savings per utilizer per month in medical benefit costs.
- Among ELX/TEZ/IVA new initiators with no previous CFTR treatment history, all-cause direct total cost of care increased 3-fold despite clinically meaningful reductions in health resource utilization, pulmonary exacerbations and total medical benefit spend. For every $7.64 in new pharmacy benefit spend, there was $1 in medical benefit cost avoided.
- These findings are consistent with previous analyses showing CFTR therapy direct costs exceed demonstrated direct medical care cost reductions.[8]
- Employers and insurers need more real-world drug therapy value data to determine fair ELX/TEZ/IVA pricing.

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