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# Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with Phe508del mutation: Evidence from randomized controlled trials

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## Abstract

**Objective:** This study aimed to conduct a systematic review and meta-analysis of randomized controlled trials to evaluate the effects of elexacaftor–tezacaftor–ivacaftor (ELX-TEZ-IVA) on patients with cystic fibrosis (CF).

**Methods:** A systematic search was performed in PubMed, Embase, and the Cochrane Library from inception to August 1, 2022. Meta-analysis was conducted using Review Manager 5.3 software.

**Results:** Six studies comprising seven reports involving a total of 1125 CF patients were included. The meta-analyses indicated that ELX-TEZ-IVA significantly improved the percentage predicted forced expiratory volume in 1 s (ppFEV1) by 10.29% (95% confidence interval (CI) (6.44, 14.14), $p < 0.00001$) and the CF questionnaire-revised respiratory domain (CFQ-R RD) by 14.59 points (95% CI (9.25, 19.94), $p < 0.00001$) compared to placebo, ivacaftor (IVA), or tezacaftor–ivacaftor (TEZ-IVA). In addition, the ELX-TEZ-IVA group showed significantly lower sweat chloride concentrations by 40.30 mmol/L (95% CI (−49.85, −30.74), $p < 0.00001$). However, the incidence of adverse events in the ELX-TEZ-IVA group was slightly higher than that in the placebo, IVA, or TEZ-IVA groups.

**Conclusion:** ELX-TEZ-IVA demonstrated efficacy in improving ppFEV1, CFQ-R RD, and sweat chloride concentrations in patients with CF. However, caution should be exercised regarding the incidence of AEs, particularly mild and moderate ones.

## Keywords

elexacaftor–tezacaftor–ivacaftor, tezacaftor–ivacaftor, cystic fibrosis, Phe508del, CF transmembrane conductance regulator

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## Introduction

Cystic fibrosis (CF) is a rare genetic disease that affects multiple organs and has a significant impact on the health and lifespan of individuals. It is estimated that worldwide, approximately 70,000 people are living with CF, and 1000 new cases are reported each year.[1–3] The accumulation of thick mucus in the respiratory tract is a defining characteristic of CF and leads to respiratory distress, recurrent lung infections, and progressive lung damage, which ultimately results in premature death.[2] CF is caused by a mutation in the CF transmembrane conductance regulator (CFTR) gene, leading to the impairment or absence of CFTR protein function. The most common mutation observed is the Phe508del mutation, the vast majority of CF patients.[4–6]

CFTR protein expression is found in various organs, including the airway epithelia, paranasal sinuses, pancreas, gut epithelia, biliary tree epithelia, vas deferens epithelia, and sweat duct epithelia.[4,5] Notably, the airway epithelia exhibit the highest levels of CFTR expression. In recent years, therapeutic approaches have focused on correcting the

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structural and functional abnormalities of the CFTR protein. Several medications have been developed to target CF by addressing these abnormalities.[7,8] CFTR modulators, such as ivacaftor (IVA), lumacaftor–ivacaftor (LUM-IVA), tezacaftor–ivacaftor (TEZ-IVA), and elexacaftor–tezacaftor–ivacaftor (ELX-TEZ-IVA), have been introduced as a new class of drugs that aim to correct the fundamental defect in the CFTR protein, although the precise mechanism is still being explored.[9,10] For individuals with common mutations like Phe508del, these medications have shown life-transforming potential and may even prevent serious complications if initiated early in childhood.[2,11,12] ELX-TEZ-IVA, a triple combination of CFTR modulators, is deemed a transformative therapy for the vast majority of individuals with CF globally.[13] In 2019, the US Food and Drug Administration and European Medicines Agency approved the combination drug ELX-TEZ-IVA as a triple-combination CFTR modulating therapy for the treatment of CF.[14] ELX-TEZ-IVA has been approved for patients aged 12 years and older who carry at least one Phe508del mutation in the CFTR gene, which accounts for approximately 90% of the CF population. Prior to starting treatment, CF gene mutation testing should be conducted if the patient's genotype is unknown.

Clinical trials have demonstrated the superior efficacy of ELX-TEZ-IVA compared to existing therapies in terms of lung function, quality of life, sweat chloride reduction, and reduction of exacerbations.[15,16] Although ELX-TEZ-IVA represents a significant advancement in CF treatment, approximately 10% of the CF population may not be eligible for this or any other CFTR modulation therapy.[15] Common adverse events (AEs) observed in clinical trials include rash and headache, and it is recommended to monitor liver function during treatment.[15] Moreover, the modulators have been deemed safe when combined with other drug administrations.[17,18] Continued assessment of patient data is necessary to establish the long-term safety and efficacy of this therapy. In this study, we conducted a comprehensive systematic review and meta-analysis of all available randomized controlled trials (RCTs) to evaluate the efficacy and safety of ELX-TEZ-IVA in individuals with CF.

## Methods

### Search strategy and data extraction

This meta-analysis study was conducted following the guidelines outlined in the PRISMA protocol.[10] A systematic search was performed in PubMed, Embase, and the Cochrane Library from inception up to August 1, 2022, with articles in the English language. The search terms used included "elexacaftor-tezacaftor-ivacaftor" [MeSH], "Trikafta," and "VX-445-tezacaftor-ivacaftor." The included RCTs enrolled CF patients and assessed the effectiveness and safety of ELX-TEZ-IVA. Two researchers independently screened the titles and abstracts of the literature for preliminary selection and reviewed the full texts of the selected articles. Any disagreements were resolved through discussion with a third researcher. Information such as authorship, publication date, ELX-TEZ-IVA and comparator dose regimens, study design, therapy duration, study site, study population, outcomes, and so on were independently extracted from the included studies by the two researchers, using a standardized data collection form.

### Outcomes

The primary outcome measures included the percentage predicted forced expiratory volume in 1 s (ppFEV1), sweat chloride concentration, and the CF questionnaire-revised respiratory domain (CFQ-R RD). The secondary outcome measures encompassed safety, including any AEs, serious adverse events (SAEs), AEs leading to discontinuation of the drug, and the most frequently reported AEs.

### Statistical analysis

In this study, we used Review Manager 5.3 software to perform statistical analysis. To assess the quality of the included studies and investigate any potential publication bias, we employed the Cochrane Collaboration's bias assessment tool. For the analysis of data, we calculated the mean difference (MD), odds ratio (OR) as the effect analysis statistic, and 95% confidence interval (CI). We conducted a chi-square test and quantitatively assessed heterogeneity using the $I^2$ statistic. To evaluate the robustness of our findings, we conducted a sensitivity analysis using a leave-one-out approach. The significance level for the meta-analysis was set at 0.05, indicating that a $p$-value of less than 0.05 was considered statistically significant.

## Results

### Searching results and study characteristics

A total of 792 articles were initially searched, including those from the Cochrane Library ($n=1$), PubMed ($n=196$), and Embase ($n=595$). After removing duplicate literature using EndNote X8 software ($n=125$), the remaining articles were read for screening. Eventually, six RCTs were included, consisting of seven reports[19–24] that met the inclusion criteria (Figure 1). These studies involved a total of 1125 patients with CF. Among the included patients, there were 563 males and 562 females, with an average age of $27.70 \pm 13.59$ years. In the ELX-TEZ-IVA group, there were 576 patients, while in the IVA, TEZ-IVA, or placebo group, there were 549 patients (Table 1).

The quality assessment of the seven reports is provided in Figures 2 and 3. Four RCTs adequately described the randomization methods, allocation concealment, blinding of participants and personnel, and incomplete outcome data, with a

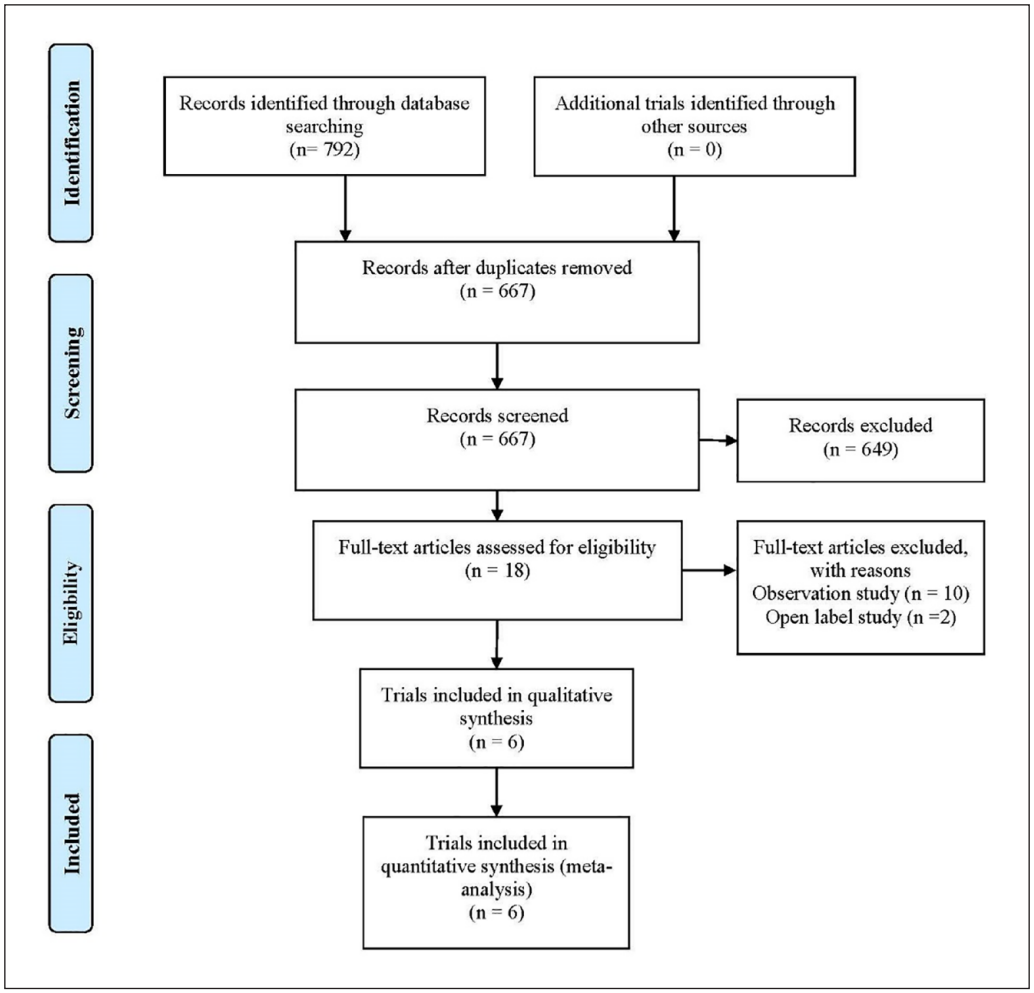


**Figure 1.** PRISMA flowchart.

low risk of bias. Three RCTs lacked detailed information on randomization methods and allocation concealment, indicating a high risk of bias. Two RCTs were open label and had a high risk of bias.

## *Efficacy analysis*

The available data from seven reports showed that the combination treatment of ELX-TEZ-IVA significantly increased ppFEV1 compared to placebo, IVA, or TEZ-IVA. The meta-analyses revealed a remarkable increase of 10.29% (95% CI (6.44, 14.14), $p < 0.00001$, $I^2 = 95\%$) in ppFEV1 with ELX-TEZ-IVA (Figure 4). In a sensitivity analysis where the data from the study by Barry et al.[23] were removed, the heterogeneity decreased from 95% to 55%. The results of the sub-analysis showed that ELX-TEZ-IVA increased ppFEV1 compared to placebo by 13.44% (95% CI (11.97, 14.90), $p < 0.00001$, $I^2 = 0\%$) in F/MF patients and by 8.33% (95% CI (3.95, 12.72), $p < 0.00001$, $I^2 = 93\%$) compared to IVA or TEZ-IVA. When excluding the data from the study by Barry et al.,[23] the heterogeneity decreased from 93% to 0%.

All included studies provided values of CFQ-R RD, and a meta-analysis of the available data revealed a significant improvement of 14.59 points (95% CI (9.25, 19.94), $p < 0.00001$, $I^2 = 87\%$) between treatment with ELX-TEZ-IVA and placebo, IVA, or TEZ-IVA (Figure 5). The results of the sub-analysis showed that ELX-TEZ-IVA versus placebo led to an improvement of 15.23 points (95% CI (3.65, 26.81), $p = 0.01$, $I^2 = 94\%$) in F/MF patients, and versus IVA or TEZ-IVA, it resulted in an improvement of 14.12 points (95% CI (8.64, 19.59), $p < 0.00001$, $I^2 = 72\%$) in F/F patients. In the sensitivity analysis, the data from the study by Marcus et al.[24] were removed, and this resulted in a decrease in heterogeneity from 94% to 0%. Similarly, when the data from the study by Barry et al.[23] were removed, the heterogeneity decreased from 72% to 0%.

In addition, the sweat chloride concentrations were significantly lower in the ELX-TEZ-IVA group compared to the placebo, IVA, and TEZ-IVA groups. The meta-analysis of available data revealed a significant reduction of 40.30 mmol/L (95% CI (−49.85, −30.74), $p < 0.00001$, $I^2 = 96\%$) between the ELX-TEZ-IVA group and the placebo,

**Table 1.** The baseline characteristic of the included study.

| Study, year published | Intervention | | Patients number | Study duration | Therapy duration | Study design | Study population | Study site | Male (%) | Mean ± SD age (years) |
|---|---|---|---|---|---|---|---|---|---|---|
| | F/MF | F/F | | | | | | | | |
| Keating et al.[19] | Placebo | | 12 | July 2017 to March 2018 | 4 weeks | Phase 2 | ⩾ 18 years | 38 sites in 4 countries | 10 (83) | 29.7 ± 7.5 |
| | ELX-TEZ-IVA | | 21 | | | | | | 10 (48) | 33.3 ± 10.3 |
| | | TEZ-IVA | 7 | | | | | | 6 (86) | 27.9 ± 8.0 |
| | | ELX-TEZ-IVA | 21 | | | | | | 12 (57) | 29.9 ± 7.6 |
| Heijerman et al.[20] | | TEZ-IVA | 52 | August to December 2018 | 4 weeks | Phase 3 | ⩾ 12 years | 44 sites in 4 countries | 24 (46) | 27.9 ± 10.8 |
| | | ELX-TEZ-IVA | 55 | | | | | | 24 (44) | 28.8 ± 11.5 |
| Middleton et al.[21] | Placebo | | 203 | June 2018 to April 2019 | 24 weeks | Phase 3 | ⩾ 12 years | 115 sites in 13 countries | 105 (52) | 26.8 ± 11.3 |
| | ELX-TEZ-IVA | | 200 | | | | | | 104 (52) | 25.6 ± 9.7 |
| Barry et al.[23] | | IVA or TEZ-IVA | 126 | August 2019 to June 2020 | 8 weeks | Phase 3 | ⩾ 12 years | 96 sites in 13 countries | 65 (51.6) | 37.6 ± 14.3 |
| | | ELX-TEZ-IVA | 132 | | | | | | 65 (49.2) | 37.7 ± 14.7 |
| Sutharsan et al.[22] | | TEZ-IVA | 88 | October 2019 to July 2020 | 24 weeks | Phase 3b | ⩾ 12 years | 35 sites in 4 countries | 43 (49) | 27.8 ± 11.0 |
| | | ELX-TEZ-IVA | 87 | | | | | | 44 (51) | 27.9 ± 11.8 |
| Mall et al.[24] | Placebo | | 61 | June 2020 to May 2021 | 24 weeks | Phase 3b | 6–11 years | 34 sites in 10 countries | 26 (43) | 9.2 ± 1.7 |
| | ELX-TEZ-IVA | | 60 | | | | | | 25 (42) | 9.1 ± 1.8 |

F/MF: Phe508del–minimal function; F/F, Phe508del–Phe508del; ELX, elexacaftor; TEZ, tezacaftor; IVA, ivacaftor; TEZ-IVA, tezacaftor–ivacaftor; ELX-TEZ-IVA, elexacaftor–tezacaftor–ivacaftor.




**Figure 2.** Graphs of risk of bias for six studies.

IVA, or TEZ-IVA groups (Figure 6). In the sensitivity analysis, when the data from the study by Barry et al.[23] were removed, the heterogeneity decreased from 96% to 69%. The results of the sub-analysis showed that in F/MF patients, ELX-TEZ-IVA led to a reduction of 44.12 mmol/L (95% CI (−54.81, −33.42), $p < 0.00001$, $I^2 = 75\%$). In F/F patients, ELX-TEZ-IVA resulted in a reduction of 38.12 mmol/L (95% CI (−50.23, −26.02), $p < 0.00001$, $I^2 = 97\%$). In the sensitivity analysis, when the data from the study by Marcus et al.[24] were removed, the heterogeneity decreased from 75% to 0%. Similarly, when the data from the study by Barry et al.[23] were removed, the heterogeneity decreased from 97% to 0%.

## *Safety analysis*

The results of the study showed that the incidence of AEs in the ELX-TEZ-IVA group was slightly higher than that in the placebo, IVA, or TEZ-IVA groups (Figure 7). However, this difference was not statistically significant (OR = 0.76, 95% CI (0.55, 1.06), $p = 0.11$). On the other hand, there was a statistically significant lower incidence of SAEs in the ELX-TEZ-IVA group compared to the other groups (OR = 0.55, 95% CI (0.38, 0.79), $p = 0.001$). There were no significant differences in the incidence of AEs leading to drug discontinuation between the ELX-TEZ-IVA group and

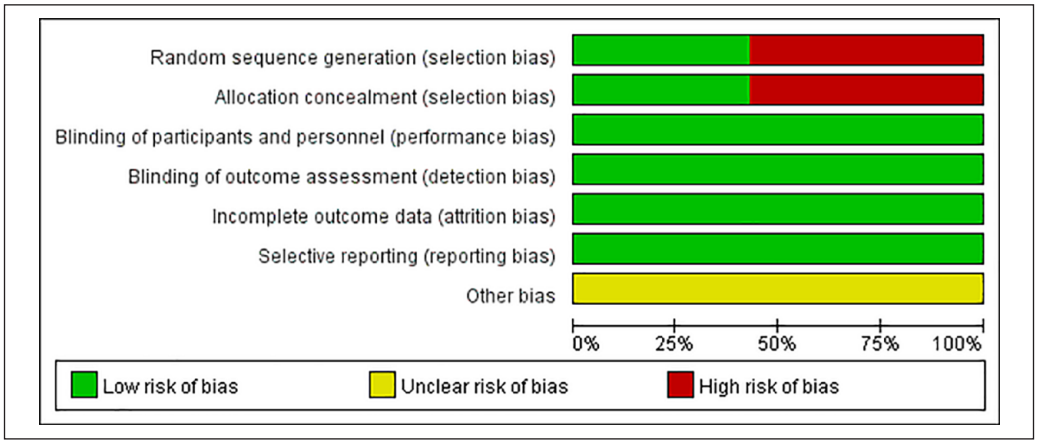


**Figure 3.** Quality assessment for risk of bias for six studies.

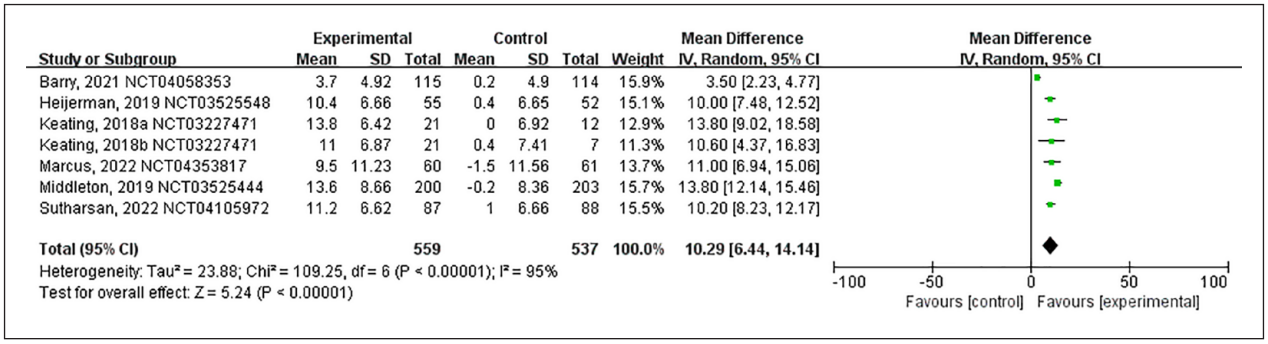


**Figure 4.** Forest plots of RCTs illustrating MD in ppFEV1.

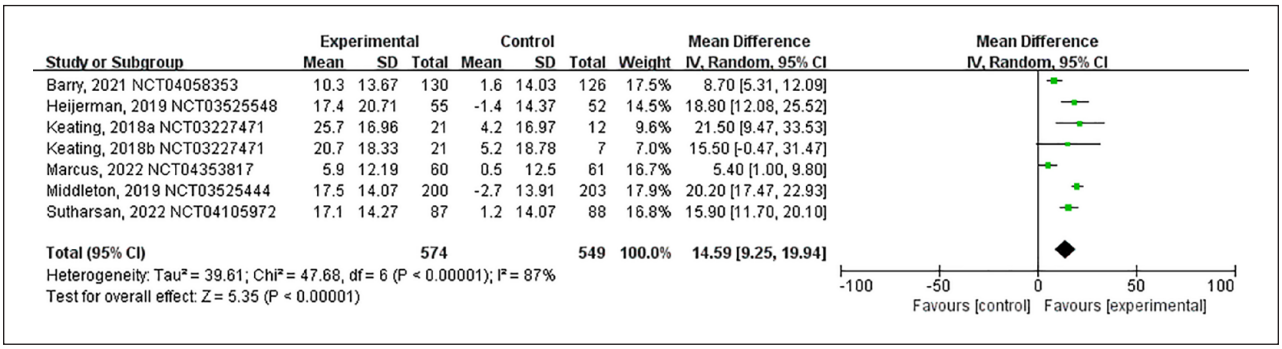


**Figure 5.** Forest plots of RCTs illustrating MD in CFQ-R RD.

the other groups (OR = 0.99, 95% CI (0.33, 2.97), $p = 0.99$). When comparing the ELX-TEZ-IVA group with the placebo group, there were no statistically significant differences in SAEs (OR = 1.08, 95% CI (0.65, 1.77), $p = 0.77$). However, there were statistically significant differences in mild and moderate AEs (OR = 1.28, 95% CI (1.00, 1.63), $p = 0.05$) and no significant differences in severe AEs (OR = 1.08, 95% CI (0.65, 1.77), $p = 0.99$, Figure 8). No deaths occurred during the trial and there were some common AEs reported in all included studies, such as oropharyngeal pain, cough, nasopharyngitis, headache, increased sputum, infective pulmonary exacerbation of CF, and upper respiratory tract infection (Table 2).

## Discussion

CF is a genetic disorder caused by mutations in the CFTR gene, which leads to dysfunctional CFTR protein.[2,4,14] This condition primarily affects lung function and manifests as chronic airway infection and inflammation.[25] Several drugs have been developed to alleviate the clinical symptoms of CF and improve lung function. One such drug is

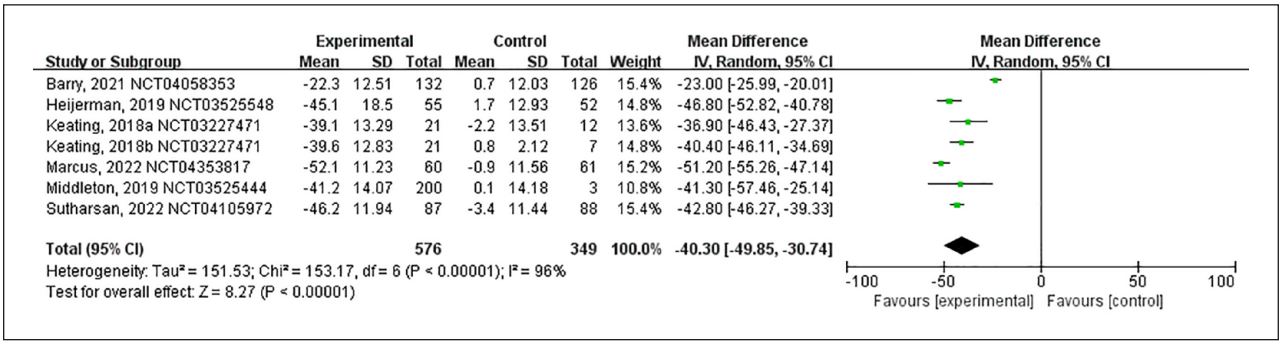


**Figure 6.** Forest plots of RCTs illustrating MD in sweat chloride concentrations.

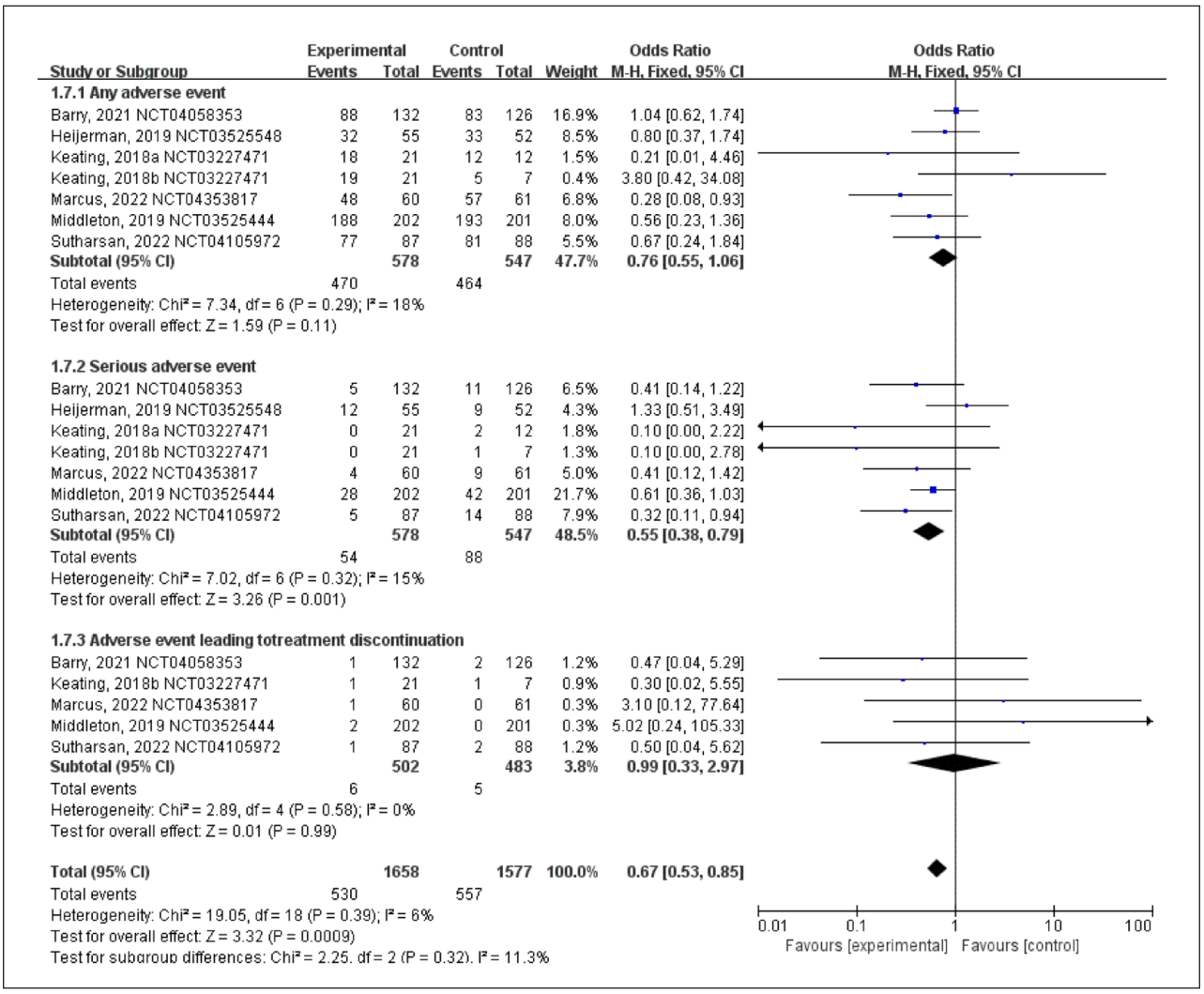


**Figure 7.** Forest plots of RCTs illustrating the OR of any AEs, SAEs, and AEs leading to treatment discontinuation.

ELX-TEZ-IVA, the first triple-combination CFTR modulating therapy consisting of two correctors and a CFTR channel potentiator. This treatment is specifically targeted for CF patients with at least one Phe508del mutation in the CFTR gene.[26] In this meta-analysis, we aimed to evaluate the efficacy and safety of ELX-TEZ-IVA in CF patients. Most studies have reported positive outcomes for CF patients with specific CFTR gene configurations.

Our findings revealed that ELX-TEZ-IVA led to a remarkable increase of 10.29% in ppFEV1 compared to placebo,

**Table 2.** The results of safety in meta-analysis.

| Outcomes | Participants | | $I^2$ | Effect estimate | *p* Value |
|---|---|---|---|---|---|
| | ELX-TEZ-IVA arm | Comparator arm | | | |
| Oropharyngeal pain | 41/578 | 47/547 | 45% | 0.82 (0.53, 1.27) | 0.36 |
| Cough | 84/578 | 150/547 | 67% | 0.56 (0.29, 1.11) | 0.10 |
| Nasopharyngitis | 55/578 | 51/547 | 0% | 1.04 (0.69, 1.56) | 0.86 |
| Headache | 94/578 | 86/547 | 31% | 1.08 (0.78, 1.48) | 0.66 |
| Sputum increased | 76/578 | 72/547 | 0% | 0.96 (0.67, 1.37) | 0.81 |
| Infective pulmonary exacerbation of CF | 86/578 | 171/547 | 17% | 0.25 (0.18, 0.35) | <0.00001 |
| Upper respiratory tract infection | 37/344 | 29/341 | 0% | 1.30 (0.78, 2.17) | 0.31 |

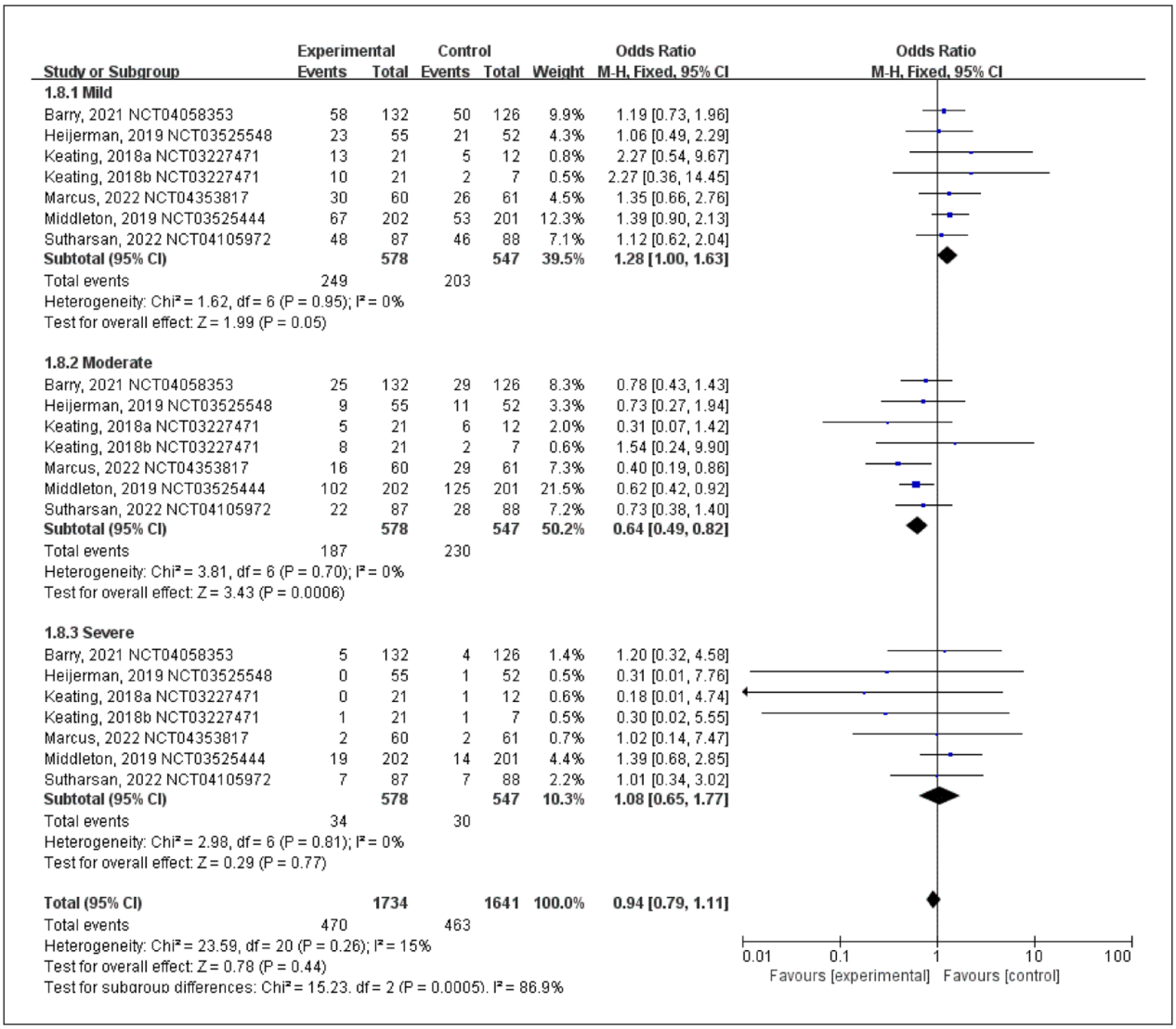


**Figure 8.** Forest plots of RCTs illustrate the OR of mild, moderate, and severe AEs.

IVA, or TEZ-IVA. In addition, we observed significant improvements in ppFEV1 of 13.44% in F/MF patients compared to placebo and 8.33% in F/F patients compared to IVA or TEZ-IVA. These results are consistent with previous studies conducted by Nichols et al.,[27] Zemanick et al.,[28] and Southern et al.,[29] where ppFEV1 improvements ranged from 9.76% to 14.3% in F/MF patients and from 10.0% to 10.2% in F/F individuals. These findings suggest that ELX-TEZ-IVA can

effectively improve lung function in CF patients, particularly in those with specific CFTR gene configurations.

The CFQ-R RD is a validated patient-reported outcome measure that assesses health-related quality of life in individuals with CF across various domains. The results of the meta-analysis indicated that ELX-TEZ-IVA significantly improved the CFQ-R RD by 14.59 points. In specific CFTR gene configurations, ELX-TEZ-IVA led to improvements of 15.23 points in F/MF patients compared to placebo and 14.12 points in F/F patients compared to IVA or TEZ-IVA. These findings are consistent with previous studies by Zemanick et al.[28] and Nichols et al.,[27] which reported improvements of 7.0 points and 20.4 points, respectively.

Sweat chloride concentration is a clinical indicator of CFTR function and is used to diagnose CF. Lower sweat chloride concentrations are associated with better disease outcomes and improved lung function. The meta-analysis demonstrated that ELX-TEZ-IVA significantly decreased sweat chloride concentrations by −40.30 mmol/L. In specific CFTR gene configurations, ELX-TEZ-IVA led to reductions of −44.12 mmol/L in F/MF patients compared to placebo and −38.12 mmol/L in F/F patients compared to IVA or TEZ-IVA. These findings align with studies by Nichols et al.,[27] which reported a decrease of 41.7 mmol/L, and other studies with mean reductions of 60.9[28] and 60 mmol/L.[16]

In terms of safety, there was a statistically significant difference in the incidence of SAEs. Specifically, the ELX-TEZ-IVA group exhibited a lower frequency of SAEs compared to other groups. In addition, the ELX-TEZ-IVA treatment exhibited significant differences in mild and moderate AEs compared to the placebo. Similar to the study by Nikoletta et al.,[30] the results indicated that this new ELX-TEZ-IVA has an overall favorable safety profile, with mild to moderate AEs. Among the participants, a majority experienced mild or moderate AEs,[22,31] and there were no differences in the number or severity of AEs between ELX-TEZ-IVA and placebo or control.[29] SAEs were observed in 6% of participants in the ELX-TEZ-IVA group and 16% of participants in the TEZ-IVA group.[22] None of the studies reported any deaths.[19–24,29] It was reported in a study that 1% of patients in the ELX-TEZ-IVA group discontinued treatment due to AEs.[16] Moreover, among the SAEs, infective pulmonary exacerbations of CF, hemoptysis, and distal intestinal obstruction syndrome were found to be more common.[31]

Various AEs were reported in the studies, including oropharyngeal pain, cough, nasopharyngitis, headache, increased sputum, infective pulmonary exacerbation of CF, and upper respiratory tract infection. However, no significant differences were found between ELX-TEZ-IVA and IVA, TEZ-IVA, or placebo. The most common AEs included infective pulmonary exacerbations of CF, cough, and oropharyngeal pain.[31] Elevated transaminase levels were observed in 7.1% of participants but meta-analyses were not conducted due to the rarity of events. Some neurocognitive AEs were also identified with CFTR modulators.[9,22] Other AEs reported in real-world studies included biliary colic,[32] testicular pain,[33] transaminitis,[9] and mental health-related AE.[34] Not only safe for the normal population but for the pregnant women during the second and third trimesters, ELX-TEZ-IVA also reduced the occurrence of major obstetric complications and improved respiratory status. In addition, the patient successfully delivered a healthy neonate.[17,35] There are limitations to this study, including the funding source being primarily from pharmaceutical companies and the inclusion of small and selected populations in some RCTs, which may introduce reporting bias.

## Conclusion

In conclusion, the findings from this study suggest that ELX-TEZ-IVA is an effective treatment for CF patients. It shows significant improvements in lung function (ppFEV1), health-related quality of life (CFQ-R RD), and CFTR function (sweat chloride concentrations). However, it is important to remain vigilant about the incidence of SAEs and mild to moderate AEs. Further monitoring and assessment of the safety profile of ELX-TEZ-IVA are necessary to ensure its long-term efficacy and safety in CF patients.

### Author contributions

ZD and BY were responsible for conducting the literature searches and selecting the relevant studies. RH analyzed the data and wrote the initial draft of the manuscript. FL designed the study and contributed to revising the manuscript. All authors have reviewed and provided approval for the final version of the manuscript.

### Declaration of conflicting interests

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### Supplemental material

Supplemental material for this article is available online.

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