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Health Technology Assessment (HTA)

Health economic evaluation

Trikafta® for the treatment of patients with cystic fibrosis: an exploratory economic evaluation

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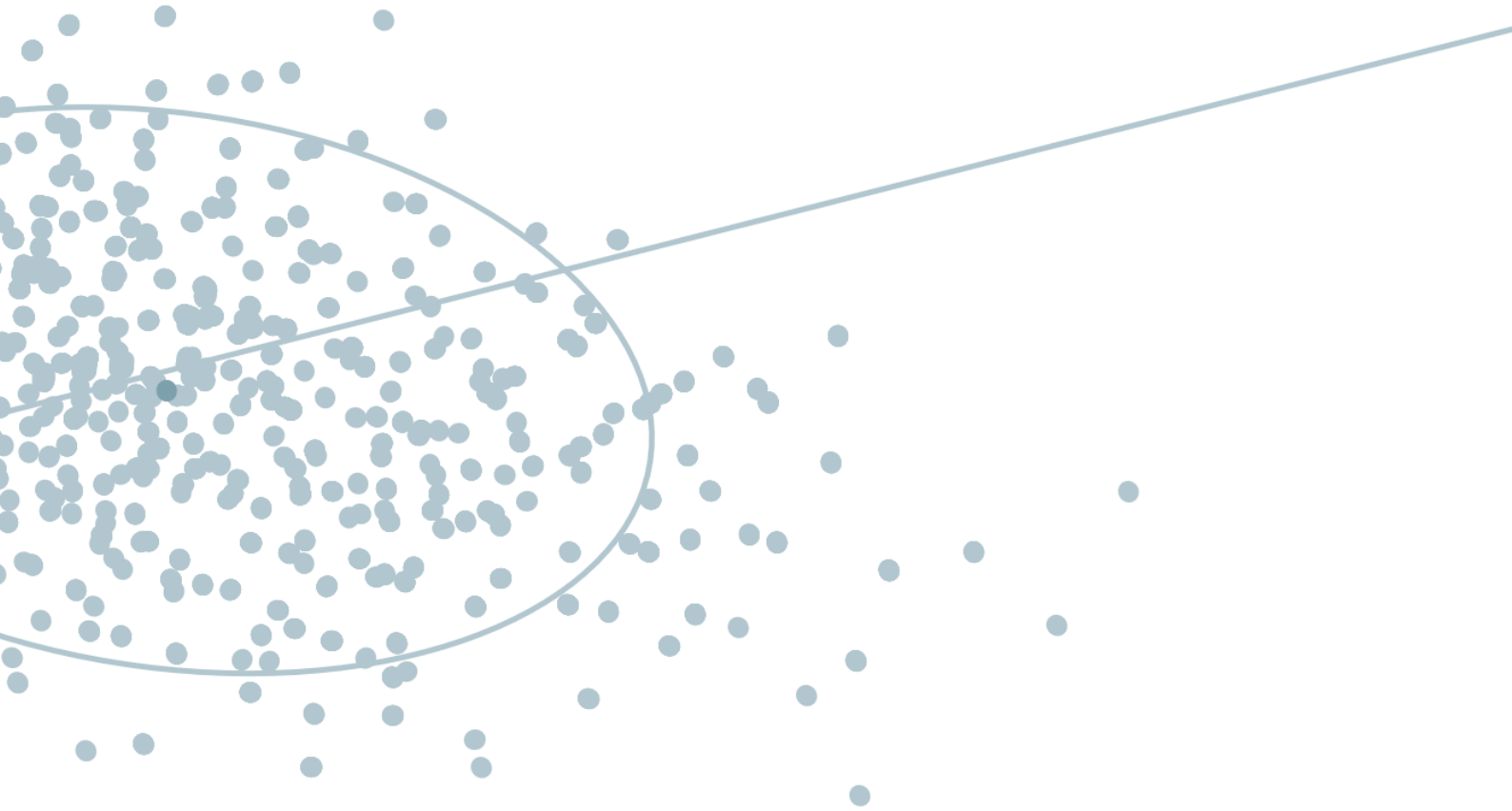

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The authors have no financial, academic, personal or any other conflicts of interest to declare in relation to this project.

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Cover image: Simplified representation of a fictional probabilistic sensitivity analysis on a cost-effectiveness plane with the diagonal willingness-to-pay line.

Executive Summary

Introduction

The drug Trikafta® (ivacaftor, tezacaftor and elexacaftor) is indicated for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. It is temporarily listed on the specialty list and reimbursed by the mandatory health insurance until January 31, 2024. As part of the reimbursement review, the Federal Office of Public Health (FOPH) engaged a third party to analyze the cost-effectiveness and budget impact of Trikafta® in Switzerland to treat patients aged 6 years and older.

Methods

To provide relevant input for the economic analysis of this report, a pragmatic systematic literature review was done to evaluate the efficacy and safety of Trikafta®. A systematic literature review for economic evaluations is also performed. Targeted searches were performed for specific input variables, such as quality of life. The information from this literature review and the critical assessment performed by other health technology assessment (HTA) assessors provide information to set up an (exploratory) economic evaluation for the Swiss setting.

Results clinical literature review

Three RCTs compared Trikafta® with standard of care (placebo) in patients aged 6 and older with cystic fibrosis who have one F508del mutation and one minimal function mutation in the CFTR gene (F/MF). In addition, for patients aged 6 and older with cystic fibrosis who are homozygous for F508del mutation (F/F), a network meta-analysis is available comparing Trikafta® with standard of care (placebo). These RCTs and the network meta-analysis provide consistent high-quality evidence for the efficacy of Trikafta® in comparison with standard of care up to 24 weeks for the outcomes reported in the trials. Beyond 24 weeks, an open-label extension of two RCTs provides non-randomized follow-up data up to 48 weeks, and appears to confirm the effectiveness of Trikafta®. Trikafta® also has been shown to be a safe intervention (with follow-up up to 96 weeks), with most of the reported adverse events being related with the underlying disease (i.e. cystic fibrosis). Adverse events that warrant attention are psychiatric disorders, headache and gastrointestinal symptoms because of frequency, and rash, hepatic adverse events and distal intestinal obstruction syndrome because of severity.

No studies were identified for the following populations and/or outcomes: RCTs that compare Trikafta® with standard of care (placebo) in patients aged 6 and older with cystic fibrosis who are homozygous for F508del mutation (F/F), who have one F508del mutation and one residual

function mutation in the CFTR gene (F/RF), or who have one F508del mutation and one gating mutation in the CFTR gene (F/G); data on mortality as an efficacy outcome; data on quality of life measured with a generic utility instrument; effectiveness data based on RCTs beyond 24 (- 48) weeks; safety data beyond 96 weeks.

Exploratory economic evaluation

For the economic part, we note that there are a lot of large uncertainties for calculating the cost-effectiveness of Trikafta®. The presence of uncertainty is common in economic evaluations. However, in this case, there is high uncertainty for all key variables: the magnitude of the impact on mortality, the (longer-term) impact on ppFEV1 and the associated impact on quality of life and disease management costs. These major uncertainties were also highlighted in previous HTA reports.

To deal with these uncertainties, several scenarios were developed modelling hypothetical mortality hazard ratios. Based on information from previous HTA reports, assumptions were also modelled regarding the impact on the decline in ppFEV1, QoL, disease management costs and lung transplants. Results were also calculated for different time horizons, discount rates for costs and effects and Trikafta® price discounts. Given the high uncertainty for the different input variables, it was not possible to indicate one specific base case analysis. The results for the different scenarios were presented side by side with the intention of displaying the possible ICERs and identifying the most determining variables.

Across all scenarios (excluding two discount rate scenarios), when applying the official list price for Trikafta®, there was no average ICER that was lower than CHF1 million per quality-adjusted life year (QALY) gained. This result was in line with the results of three of the four identified HTA reports. The main reason is the annual cost of about CHF228 000 per patient and the chronic use of this intervention. Only when combining a number of 'optimal' scenarios (a mortality hazard ratio of 0.1, an optimistic evolution in ppFEV1 and a lower disease management cost when using Trikafta®) and a price discount of 90%, an ICER of about CHF100 000 per QALY gained was obtained.

Given the large uncertainties regarding several determining variables, future research on the (longer-term) impact of Trikafta® on mortality, ppFEV1, quality of life and disease management costs may shed more light on the cost-effectiveness of this intervention. Notwithstanding, the exploratory scenario analyses performed show that the cost-effectiveness is mainly determined by the annual recurrent cost for Trikafta®.

Swiss-specific data are available describing the number of homozygous and heterozygous patients. At the official list price, the total budget impact over 5 years for treating 69 F508del

homozygous patients aged 6-11 years would be about CHF78 million. This would become about CHF55 million if substitution costs for other CFTR modulators (Kalydeco®, Orkambi® and Symdeko®) are taken into account. For treating another 70 F508del heterozygous patients aged 6-11 years, the total budget impact over 5 years would be about CHF79 million or CHF78 million, without and with inclusion of substitution costs, respectively. This budget impact should not be separated from the potential budget impact to treat patients over 12 years old (305 homozygous and 266 heterozygous patients). Under full market penetration, treating all homozygous patients (n = 374) with Trikafta® would result in a 5-year budget impact of about CHF426 million (or CHF397 million after subtraction of substitution costs). This would be CHF383 million or CHF368 million, respectively, for treating 336 heterozygous patients.

Conclusion

The evidence on short-term outcomes provides consistent high-quality evidence for the efficacy of Trikafta®. However, evidence on important outcomes such as mortality, the (longer-term) impact on ppFEV1 and the associated impact on quality of life and disease management costs is lacking. Notwithstanding, the exploratory economic evaluation shows that ICERs exceed CHF1 million per QALY gained in just about all scenarios. Only in an 'optimal' scenario in combination with a 90% price discount, the ICER potentially approaches about CHF100 000 per QALY gained. The budget impact depends, among other things, on the target population to be taken into account. Both cost-effectiveness and budget impact are mainly determined by the annual cost of Trikafta® and its chronic use.

Table of Contents

List of tables

Table Of Figures

Abbreviations and acronyms

AE	Adverse event
AIC	Akaike information criterion
ALT	Alanine transaminase
AST	Aspartate transaminase
BIA	Budget-impact analysis
BIC	Bayesian information criterion
BMI	Body mass index
BSC	Best supportive care
C	Cost
CADTH	Canadian Agency for Drugs & Technologies in Health
CDEC	Canadian Drug Expert Committee
CEESP	Commission de l'évaluation économique et de santé publique
CF	Cystic fibrosis
CFFPR	Cystic Fibrosis Foundation Patient Registry
CFQ-R	Cystic Fibrosis Questionnaire–Revised
CFTR	Cystic fibrosis transmembrane conductance regulator
CoI	Conflict of interest
CPI	Consumer price index
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
DRG	Diagnosis-related group
E	Effect
ECFS	European Cystic Fibrosis Society
ECFSPR	European Cystic Fibrosis Society Patient Registry

ELX	Elexacaftor
ELX/TEZ/IVA	Elexacaftor-tezacaftor-ivacaftor
EQ-5D	EuroQol 5-dimensions questionnaire
EQ-5D-3L	EuroQol 5-dimensions 3-level questionnaire
EUnetHTA	European network for Health Technology Assessment
FEV1	Forced expiratory volume in 1 second
F/F	Homozygous for F508del mutation in the CFTR gene
F/G	1 F508del mutation and 1 gating mutation in the CFTR gene
F/MF	1 F508del mutation and 1 minimal function mutation in the CFTR gene
F/RF	1 F508del mutation and 1 residual function mutation in the CFTR gene
FOPH	Federal Office of Public Health
GBA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAS	Haute Autorité de Santé
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IC	Incremental costs
ICER	Incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review
ICTRP	International Clinical Trials Registry Platform
IE	Incremental effects
INAHTA	International Network of Agencies for Health Technology Assessment
INESSS	Institut National d'Excellence en Santé et en Services Sociaux
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISRCTN	International Standard Randomised Controlled Trial Number
IVA	Ivacaftor

KM	Kaplan-Meier
LCI	Lung Clearance Index
LTx	Lung transplantation
LUM-IVA	Lumacaftor-ivacaftor
LY	Life years
LYG	Life years gained
MA	Meta-analysis
MD	Mean difference
NA	Not applied/Not applicable
NMA	Network meta-analysis
NR	Not reported
PEP	Positive expiratory pressure
PERT	Pancreatic enzyme replacement therapy
PICO(S)	Population, intervention, comparator, outcome, (study design)
ppFEV1	Percentage predicted forced expiratory volume in the first second
PPP	Purchasing power parities
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomized controlled trial
RR	Rate ratio
SR	Systematic review
SD	Standard deviation
TEZ	Tezacaftor
TEZ-IVA	Tezacaftor-ivacaftor
TSQM	Treatment Satisfaction Questionnaire for Medication
VAT	Value added tax

WHO	World Health Organization
ZIN	Zorginstituut Nederland

Objective of the health economic evaluation

The objective of a health economic evaluation is to generate a focused assessment in terms of costs and consequences of a health technology. The analytic methods applied to assess the value of using a health technology, their execution and the results are described. The analytical process is comparative and systematic. The domains covered in a health economic evaluation report include cost-effectiveness and budget impact. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1. Policy question and context

The drug Trikafta® (ivacaftor, tezacaftor and elexacaftor) is indicated for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. It is temporarily listed on the specialty list and reimbursed by the mandatory health insurance until January 31, 2024. As part of the reimbursement review, the Federal Office of Public Health (FOPH) engaged a third party to analyze the cost-effectiveness and budget impact of Trikafta® in Switzerland.

Originally, the request was to conduct only an economic evaluation. Given the importance of the clinical component in preparing an economic evaluation, it was suggested also to review the evidence for the intervention in the relevant indication. Given the short time frame in which the study was conducted, it was agreed to omit certain information that you would expect to find in a full health technology assessment report (e.g. more detailed information on the diagnosis, burden of the disease, existing practice guidelines for the treatment of the disease, etc.). This should be taken into account when reading this report.

2. Medical background

CF is the most common genetic disease in Europe. Mutations in the CFTR gene, which is located on chromosome 7, interfere with the regulation of ion and fluid transport across cell membranes. A dysfunction of the CFTR protein causes secretions to become sticky. This affects multiple organs, but most frequently the lungs, small and large intestines and the bile ducts. Patients present symptoms such as cough, with viscous sputum, abdominal pain and digestive problems.[1-4]

Cystic fibrosis is considered a rare disease and newborn show a risk of disease of 1:2500. Cystic fibrosis is an autosomal recessive disease and occurs only when both copies of the CFTR gene are mutated. CFTR mutations are categorized into 6 classes. Class II is defined by defective protein maturation and accelerated degradation and is associated with severe CF. The F508del mutation is typically leading to a class II CFTR mutation.[3, 4] 88% of patients with CF have at least one mutation in class II. Examples of class II mutations are the F508del (which is also the most common mutation), N1303K and I507del. CFTR protein is created, but misfolds. As a consequence, the transport of the CFTR protein to the cell surface is prevented.[5] Table 1 provides an overview of the classes and their impacts on the CFTR protein.

Table 1: Overview CFTR mutation classes

Class (% of people with CF who have at least one mutation in that class)	Impact on CFTR Protein	Mutations
Normal	CFTR protein is produced, and is transported to the cell surface. It allows a transfer of water and chloride	No mutation
Class I (22%)	No functional CFTR is created	G542X, W128X, R553X
Class II (88%)	CFTR protein is produced but misfolds, keeping it from moving to apical membrane	F508del, N1303K, I507del
Class III (6%)	CFTR protein is created and travels to the apical membrane, but the channel gate does not open properly	G551D, S549N
Class IV (6%)	CFTR protein is produced and travels to the cell surface, but the function of the channel does not work properly	D1152H, R347P, R117H
Class V (5%)	Normal CFTR protein is created and moves to the cell surface, but the function of the channel does not work properly	3849+10kbC → T, 2789+5G → A, A455E

CFTR: cystic fibrosis transmembrane conductance regulator.

Source: From the Cystic Fibrosis Foundation website: https://www.cff.org/sites/default/files/2021-12/Know-Your-CFTR-Mutations-Infographic.pdf[6]

3. Technology

3.1 Technology description

Several specific agents are available for the treatment of CF patients who have at least one F508del mutation in the CFTR gene. These agents are called CFTR potentiators and correctors. Depending on the mutation, they can improve the function of defective CFTR protein and are therefore only approved in Switzerland for certain defects of the CFTR gene.[7]

The medicine Trikafta® consists of the CFTR potentiator **ivacaftor** and the two CFTR correctors **tezacaftor and elexacaftor**:

For **ivacaftor** to be effective, CFTR proteins must be present on the cell surface, and the drug is only effective in the presence of so-called gating defects. Gating defects are mutations in the structure of the CFTR protein that cause dysfunctional CFTR protein channels.[7]

Tezacaftor can promote the formation and transport of CFTR proteins to the cell surface. Tezacaftor is used only in combination with the active ingredient ivacaftor.[7]

Elexacaftor can also promote the formation and transport of CFTR proteins to the cell surface, but in a different way than tezacaftor. This triple combination of ivacaftor, tezacaftor and elexacaftor leads to functional improvement in F508del defects.[7]

Trikafta® is indicated for the treatment of patients with CF who are 6 years of age and older and have at least one F508del mutation in the CFTR gene.[8]

Trikafta® should only be prescribed by physicians experienced in the treatment of CF. If the patient's genotype is not known, the presence of at least one F508del mutation must be confirmed by a genotyping test.[8]

Trikafta® tablets should be used for the treatment of adults, youth and children from 6 years as follows:[8]

Table 2: Recommended dosage Trikafta®

Age	Morning dose	Evening dose
6 to <12 years with a body weight <30 kg	Two tablets each containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg	One tablet of ivacaftor 75 mg
6 to <12 years with a body weight ≥30 kg	Two tablets each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	One tablet of ivacaftor 150 mg
≥12 years	Two tablets each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	One tablet of ivacaftor 150 mg

Trikafta® (Elexacaftorum 50 mg, Tezacaftorum 25 mg, Ivacaftorum 37.5 mg, Ivacaftorum 75 mg) is temporarily listed on the speciality list and reimbursed by mandatory health insurance until 31 January 2024 for the treatment of patients with CF aged 6-11 years who have at least one F508del mutation in the CFTR gene.[9]

Trikafta® (Elexacaftorum 100 mg, Tezacaftorum 50 mg, Ivacaftorum 75 mg, Ivacaftorum 150 mg) is temporarily listed on the speciality list and reimbursed by mandatory health insurance until 31 January 2024 for the treatment of patients with CF 6 years of age and older who have at least one F508del mutation in the CFTR gene.[9]

The Trikafta® therapy should only be continued after 6 and 12 months if:[9]

– there is no sustained deterioration in lung function from baseline or

– there is a reduction in the number of clinically relevant pulmonary exacerbations (with hospitalization, IV antibiotic therapy)

Further information can be found on the speciality list of the FOPH.[9]

3.2 Alternative technologies

3.2.1 Standard of care

Symptomatic CF treatment, also known as standard of care, includes treatments such as mucolytics, inhaled and oral antibiotics, inhaled hypertonic saline, nutritional supplements, enteral tube feeding, pancreatic enzymes, antifungals and corticosteroids, and physical therapy.[4]

Switzerland does not have its own recommendations for optimal therapy for children and adolescents with cystic fibrosis (CF). The Swiss recommendations for the optimal treatment of CF are based on the recommendations of the European Cystic Fibrosis Society (ECFS) Guidelines.[10]

In summary, standard CF therapy includes regular, twice-daily inhalation therapy with hypertonic saline (usually 6%) and inhalation with DNAse (Pulmozyme®), followed by secretion removal using Flutter, Acapella, positive expiratory pressure (PEP) or autogenous drainage. For the upper respiratory tract, this also includes twice-daily rinsing with saline, preferably with a nasal cannula. All CF children with pancreatic insufficiency (90%) require pancreatic enzyme replacement therapy (PERT). In addition, fat-soluble vitamins (A, D, E and K) must be taken daily (1-2 capsules per day). In case of heavy sweating or hot temperatures, additional salt substitution is required. In case of infectious pulmonary exacerbations, which are usually caused by viruses, antibiotic therapy is prescribed for 1-2 weeks. If this is not sufficient, a 10-14 day course of intravenous antibiotics in hospital is necessary. CF patients need regular professional respiratory physiotherapy, which takes place once a week to every 1-2 months, depending on the severity. (information received from a Swiss expert)

3.2.2 Symdeko® (Tezacaftor and Ivacaftor)

Symdeko® is indicated for the treatment of patients with CF 6 years of age and older who are homozygous for the F508del mutation or heterozygous for the F508del mutation and have one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, or 3849+10kbC→T.[11]

3.2.3 Kalydeco® (Ivacaftor)

Kalydeco® film-coated tablets are indicated for the treatment of CF in patients 6 years of age and older with a body weight of at least 25 kg who have an R117H CFTR mutation or one of the following gating mutations (Class III) in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.[12]

3.2.4 Orkambi® (Lumacaftor and Ivakaftor)

Orkambi® tablets are indicated for the treatment of CF in patients 6 years of age and older who are homozygous for the F508del mutation in the CFTR gene.[13]

4. Population, Intervention, Comparator, Outcome (PICO)

Table 3: PICO(S) scheme

P:	**Patients aged 6 and older with CF who have at least one F508del mutation in the CFTR gene** *Depending on the available evidence – subgroups CFTR genotype:* – *Patients aged 6 and older with CF who are homozygous for F508del mutation (F/F)* – *Patients aged 6 and older who have 1 F508del mutation and 1 minimal function mutation in the CFTR gene (F/MF)* – *Patients aged 6 and older who have 1 F508del mutation and 1 residual function mutation in the CFTR gene (F/RF)* – *Patients aged 6 and older with CF who have 1 F508del mutation and 1 gating mutation in the CFTR gene (F/G)*
I:	Trikafta® (Elexacaftor, Tezacaftor, Ivacaftor) (in addition to standard of care)
C:	Placebo or no Trikafta® (in addition to standard of care) *Remark: a comparison of the efficacy with other alternatives (Symdeko® (Tezacaftor and Ivacaftor); Kalydeco® (Ivacaftor); Orkambi® (Lumacaftor and Ivakaftor)) is out of scope for this project (although the Trikafta® arms of these studies will be included for the safety analysis).*
O:	Clinical part: percentage predicted forced expiratory volume in the first second (ppFEV1), Lung Clearance Index (LCI), pulmonary exacerbations, meeting criteria for lung transplantation, weight-for-age z-score, health-related quality of life (HRQoL), and adverse events. Economic part: total/incremental costs; total/incremental life years (LY); total/incremental quality-adjusted life year (QALYs); incremental cost-effectiveness ratio (ICER).
S	Efficacy: health technology assessment (HTA) reports, systematic reviews (SRs), randomised controlled trials (RCTs) Safety: health technology assessment reports, systematic reviews, randomised controlled trials, (prospective or retrospective) single-arm studies Economic evaluation: full economic evaluations (looking at both costs and effects of the intervention versus the relevant comparator)

PICOS: population, intervention, comparator, outcome and study design.

5. Research questions

1. Is Trikafta® (Elexacaftor, Tezacaftor, Ivacaftor) cost-effective compared to standard of care?

2. What is the budget impact of reimbursing Trikafta® (Elexacaftor, Tezacaftor, Ivacaftor) compared to no reimbursement?

6. Methodology literature review

6.1 Systematic literature review of clinical evidence

In general, a pragmatic approach was chosen, since the results from this systematic literature review primarily served as an information source for the economic analysis in this report.

6.1.1 Databases and search strategy

A comprehensive search strategy was built, integrating the search for clinical effectiveness and safety into one search. The following electronic databases were searched:

- OVID Medline (systematic reviews and primary studies)
- EMBASE (systematic reviews and primary studies)
- Cochrane Database of Systematic Reviews (systematic reviews)
- CENTRAL (primary studies)

The search strategy was built systematically using the terms from the PICOS question (see appendix 13.1). No date limit was used. The search was restricted to the following languages: English, French, German, Dutch and Italian. The search was done on July 25th, 2023.

In addition, HTA reports were looked for at individual agencies' sites (see the International Network of Agencies for Health Technology Assessment (INAHTA) Members List, Table 74 in appendix 13.4).

Reference lists of any relevant articles were checked to identify additional relevant studies/reports, also for the articles excluded after reading the full text.

Finally, a search for ongoing RCTs was done in trial registers (ClinicalTrials.gov, EU Clinical Trials Register, WHO International Clinical Trials Registry Platform (ICTRP), International Standard Randomised Controlled Trial Number (ISRCTN) Registry). The following search terms were used: Trikafta, Kaftrio, (Elexacaftor AND Tezacaftor AND Ivacaftor), (VX-445 AND Tezacaftor AND Ivacaftor). The search for ongoing trials was done on November 13th, 2023.

6.1.2 Study selection

Studies were first screened on title and abstract using the PICOS in- and exclusion criteria. The following additional criteria were applied:

- Reviews were excluded if only one electronic database was searched (because of a high risk of missing relevant studies) and/or if no quality appraisal of the included studies was reported. This approach did not increase the risk of excluding relevant studies since the reference lists were checked.
- Randomized controlled trials comparing Trikafta® with an intervention outside the scope of this project were considered for the safety analysis (if relevant data were reported).

- Single-arm studies were excluded if they only included patients with a specific safety concern (because of selection bias).

An overview of the in- and exclusion criteria is provided in Table 4.

In a second step, the remaining papers were screened by reading the full-text. If no full- text was available, the study was excluded. Reasons for exclusion after full-text reading are reported in appendix 13.2.

The selection process was done by one researcher (JV) and discussed with a second reviewer (MN) in case of doubt.

Systematic reviews and other forms of evidence synthesis were primarily used as a source of primary studies.

Table 4: In- and exclusion criteria for the systematic literature review of clinical evidence

	Inclusion criteria	Exclusion criteria
Population	Patients aged 6 and older with CF who have at least one F508del mutation in the CFTR gene	
Intervention	Trikafta® (combination treatment with Elexacaftor, Tezacaftor, and Ivacaftor)	Other (combinations of) CFTR modulators
Comparator	Placebo No Trikafta®	Efficacy analysis: Symdeko® (Tezacaftor and Ivacaftor); Kalydeco® (Ivacaftor); Orkambi® (Lumacaftor and Ivakaftor)
Outcomes	ppFEV1, LCI, Pulmonary exacerbations, Meeting criteria for lung transplantation, Weight-for-age z-score, BMI, Health-related quality of life, Adverse events	
Study design	Efficacy: HTA reports, systematic reviews, RCTs Safety: HTA reports, systematic reviews, RCTs, (prospective or retrospective) single-arm studies	General: HTA reports and reviews searching only one electronic database and/or not reporting the quality appraisal of the included studies Narrative reviews, letters, editorials, comments Efficacy: Single-arm studies Safety: Single-arm studies only including patients with a specific safety concern

BMI: Body mass index; CFTR: Cystic fibrosis transmembrane conductance regulator; HTA: health technology assessment; LCI: Lung Clearance Index; ppFEV1: percentage predicted forced expiratory volume in the first second; RCTs: randomised controlled trials.

6.1.3 Data extraction, analysis and synthesis

For each randomized controlled trial included in the effectiveness analysis, the following data were extracted: title, reference, type of study, source of funding, country and setting, sample size, duration and follow-up, details about the statistical analysis, eligibility criteria, exclusion criteria, number of participants, patient and disease characteristics (including baseline comparability), details of the intervention and comparator, outcomes as specified in the PICO (if reported), and limitations and other comments regarding the study.

For the safety analysis, the available data on the incidence of adverse events were tabulated in an overview table.

Since the included systematic reviews and HTA reports were primarily used as a source of primary studies, we only extracted their search date, included RCTs and conclusions.

Data extraction was performed by one reviewer (JV).

6.1.4 Quality appraisal of clinical studies

Quality appraisal of the included randomized controlled trials (effectiveness analysis) was done using the “Cochrane Collaboration’s tool for assessing risk of bias" version 1.[14] This was a pragmatic choice, since the added value of the current version of the appraisal tool,[15] which is more extended and elaborate, was considered to be limited.

Also because of the pragmatic approach, no formal quality appraisal was done of the systematic reviews and of the studies included for the safety analysis.

If applicable, risk of bias for the items regarding detection bias and attrition bias were assessed per class of outcomes (e.g. subjective and objective outcomes). Quality appraisal of the RCTs was performed by one reviewer (JV) and checked in the available systematic reviews and HTA reports.

6.1.5 Statistical analysis

For each population and comparison (intervention vs. comparator), the available analyses were checked. If necessary, meta-analyses were (re)done or checked according to the statistical guidelines described in the Cochrane Handbook for Systematic Reviews of Interventions using Review Manager Software (Review Manager version 5.3.5). Heterogeneity was statistically assessed with the χ^2 test and I^2 statistic. If heterogeneity was present, a random-effects model was used instead of a fixed-effect model. Studies that were clinically heterogeneous or did not present the data in sufficient detail to enable statistical pooling were summarized qualitatively. Forest plots were reported, when appropriate.

6.1.6 Grading of the evidence

For each outcome, GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) was used to grade the quality of the supporting evidence.[16] For this assessment, GRADE

for systematic reviews was used. For systematic reviews, quality of evidence refers to one's confidence in the estimates of effect. In systematic reviews, each outcome is considered separately, in contrast to guidelines, where the evidence is assessed across all outcomes and studies for a particular recommendation.

According to GRADE, the quality of evidence is classified into four categories: high, moderate, low, and very low. Quality rating for RCTs is initially considered to be of high level. The rating is then downgraded, if needed, based on the judgement of the different quality elements (Table 5). Each quality element considered to have serious or very serious risk of bias is rated down -1 or -2 steps, respectively.

GRADE evidence profiles were made for each comparison and set of outcomes, and reported in appendix 13.3.

Table 5: Factors that may lead to downgrading of RCT-based evidence in the GRADE approach

1	Serious (-1) or very serious (-2) risk of bias
2	Serious (-1) or very serious (-2) inconsistency between studies
3	Serious (-1) or very serious (-2) indirectness
4	Serious (-1) or very serious (-2) imprecision
5	(Likely) publication bias

GRADE: Grading of Recommendations, Assessment, Development and Evaluations.

6.2 Systematic literature review of economic evidence

6.2.1 Databases and search strategy

The systematic literature search was performed in two stages.

In a first stage, priority is given to the identification of HTA evaluations performed by independent HTA organisations. In July/August 2023, we checked the international HTA database of INAHTA (International Network of Agencies for Health Technology Assessment) and the websites of HTA institutes that are members of the INAHTA network. The search terms are related to Trikafta®. More details are provided in Appendix 13.4.

In a second stage, the Medline and EMBASE electronic databases are searched. It was planned to apply the 'economic studies' filter published by the Scottish Intercollegiate Guidelines Network (SIGN - https://www.sign.ac.uk/what-we-do/methodology/search-filters/) for both Medline and EMBASE. These economic terms are supplemented with terms related to Trikafta®. However, in Medline, the number of hits related to 'Trikafta' and 'Kaftrio' was limited. Therefore, in the Medline database, it was decided to go through all the identified references without adding the 'economic studies' filter, resulting in a sensitive search and increasing time efficiency. In contrast, in Embase, due to a higher number of hits linked to the intervention terms, the 'economic studies' filter was added. An overview of this search strategy is provided in Appendix 13.4.

6.2.2 Study selection

The selection of literature is carried out in two rounds. In a first round, the identified references are assessed on the basis of title, abstract and keywords. In case of doubt, the reference is selected. In a second round, references are further selected based on the full text. References of the selected articles (especially review articles) are searched for possibly missing relevant references.

Full economic evaluations, comparing both costs and effects of the relevant intervention versus a relevant alternative, are selected. Cost studies do not fall under this category (with the exception of cost minimization studies). Finally, the medical inclusion and exclusion criteria are also taken into account (i.e. reflecting the relevant population, intervention and comparator – see Table 4).

The search strategy is performed by an economist experienced in systematic reviews of economic evaluations (MN). The selection of articles is checked by a physician with specific attention for the medical selection criteria (JV). Differences are resolved by discussion and in case of any discrepancy, a third researcher is consulted to reach consensus.

6.2.3 Data extraction, analysis and synthesis

In a first step, a "data extraction sheet" is drawn up for all selected references (see Appendix). The data extraction sheets are in the language of the original study and are working documents. On the basis of this structured form, all relevant elements needed to perform an economic evaluation are identified.

The identified economic evaluations are presented in this report. The information gathered in the data extraction sheets serves as a basis for the summary tables. These overview tables present the characteristics of these studies (country, year, stated conflict of interest, discount rate, perspective), the most important input parameters (costs, quality of life, treatment effect) and the results (incremental costs (IC), incremental effects (IE), and ICERs).

In the review of economic evaluations (part 7.2), the information is presented as provided in the identified economic evaluations. The assessment of the authors of the identified HTA reports is also provided. Our own reflection on these input variables is provided when describing the input variables for the economic evaluation of Trikafta® in the Swiss setting (part 8).

6.2.4 Quality appraisal of economic studies

A formal quality appraisal is not conducted for the identified economic evaluations. The final aim in this report is to set up an economic evaluation for the Swiss context. For this purpose, the different input variables used in the identified economic evaluations of HTA organizations are presented. Each element is assessed separately to ascertain whether the info can be used for the Swiss de novo economic model or if an alternative approach is more appropriate.

7. Results literature review

7.1 Review of clinical evidence

7.1.1 Search results

The search in Medline, Embase and the Cochrane Library yielded a total of 3159 hits. After de-duplication (904 hits) and exclusion of references in a language that was not selected (17 hits), the title and abstract of 2238 unique references were screened. Of these, 2161 references were excluded, while 77 references were selected for full-text review (Figure 1). In addition, from the search for HTA reports 14 additional references were added for full-text review.

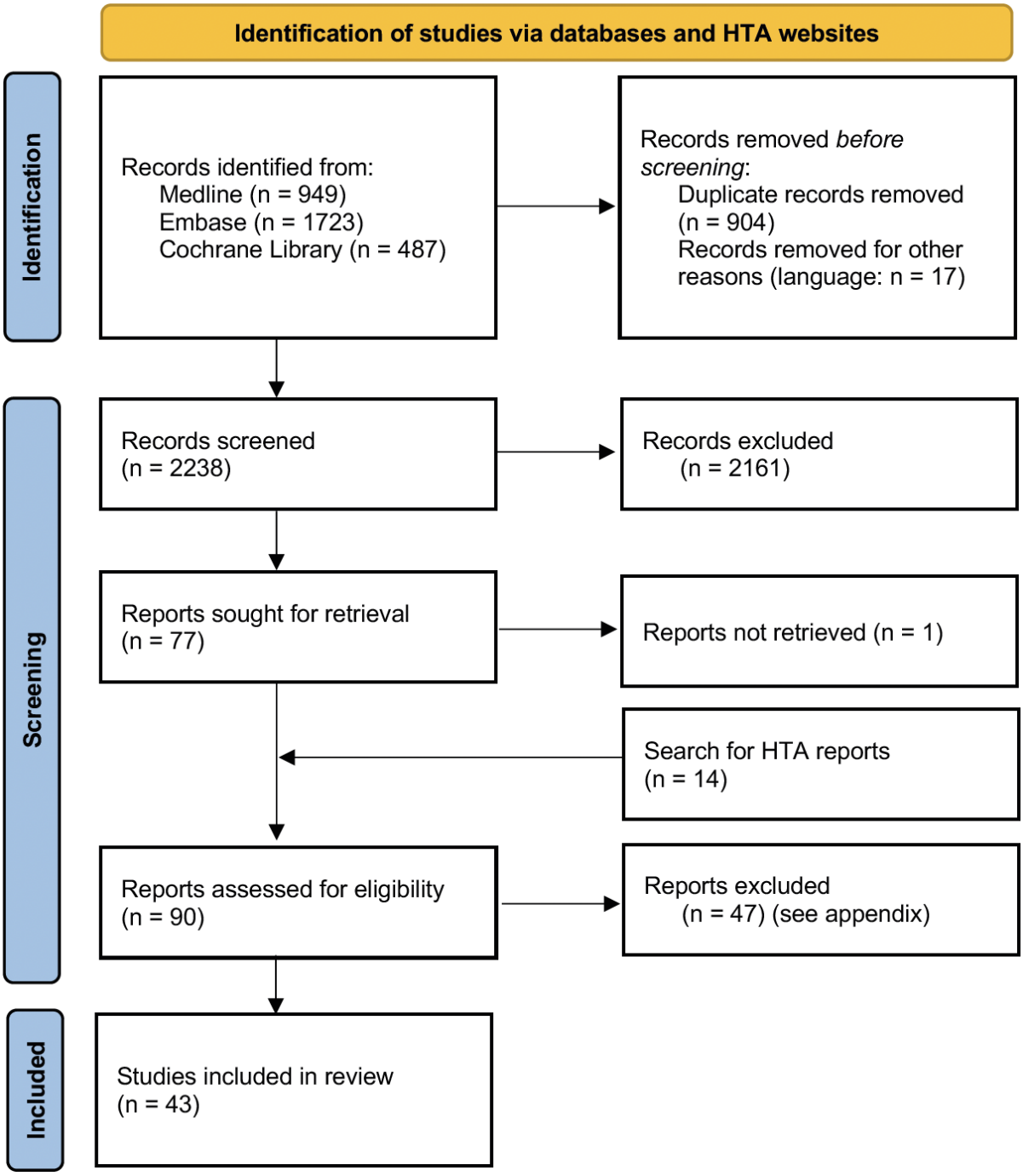
From the 91 references of which the full-text was sought for retrieval (one was not found), 48 references were excluded with reason (see appendix 13.2). The 43 included references comprised:

- Four systematic reviews:[17-20]
    - Bailey J, Rozga M, McDonald CM, Bowser EK, Farnham K, Mangus M, et al. Effect of CFTR Modulators on Anthropometric Parameters in Individuals with Cystic Fibrosis: An Evidence Analysis Center Systematic Review. J Acad Nutr Diet. 2021 07;121(7):1364-78.e2.[17]
    - Dagenais RVE, Su VCH, Quon BS. Real-world safety of cftr modulators in the treatment of cystic fibrosis: A systematic review. Journal of Clinical Medicine. 2021;10(1):1-56.[18]
    - Southern KW, Murphy J, Sinha IP, Nevitt SJ. Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del). Cochrane Database Syst Rev. 2020 12 17;12:CD010966.[19]
    - Wang Y, Ma B, Li W, Li P. Efficacy and Safety of Triple Combination Cystic Fibrosis Transmembrane Conductance Regulator Modulators in Patients With Cystic Fibrosis: A Meta-Analysis of Randomized Controlled Trials. Frontiers in Pharmacology. 2022;13.[20]
- Seven HTA reports:[4, 5, 21-25]
    - CADTH. Elexacaftor-Tezacaftor-Ivacaftor and Ivacaftor (Trikafta®). CADTH reimbursement review. Canadian Journal of Health Technologies. 2022 September 2022;2(9):383.[4]
    - Tice JA, Kuntz KM, Wherry K, Chapman R, Seidner M, Pearson SD, et al. Modulator treatments for cystic fibrosis: effectiveness and value. Evidence report: Institute for Clinical and Economic Review (ICER); 2020.[5]

- CADTH. Elexacaftor-Tezacaftor-Ivacaftor and Ivacaftor (Trikafta®). CADTH reimbursement review. Canadian Journal of Health Technologies. 2021 November 2021;1(11):248.[21]
- GBA. Ivacaftor/Tezacaftor/Elexacaftor (Kaftrio®): Gemeinsamer Bundesausschuss (G-BA); 2022 February 2022.[22]
- IQWiG. Ivacaftor/Tezacaftor/Elexacaftor und Ivacaftor (zystische Fibrose, 6 bis 11 Jahre, F508del-Mutation, MF-Mutation, heterozygot): Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG); 2022 May 2022.[23]
- ZIN. GVS-advies elexacaftor/tezacaftor/ivacaftor (Kaftrio) in combinatie met ivacaftor (Kalydeco): Zorginstituut Nederland (ZIN); 2021.[24]
- ZIN. GVS-advies elexacaftor/tezacaftor/ivacaftor (Kaftrio) in combinatie met ivacaftor (Kalydeco) – uitbreiding nadere voorwaarden: Zorginstituut Nederland (ZIN); 2022.[25]

- Six references about three different randomized controlled trials included for the effectiveness and safety analysis;[26-31]
- Four references about 3 different randomized controlled trials included for the safety analysis;[32-35]
- Twenty-two single-arm studies included for the safety analysis.[36-57]

Figure 1: PRISMA flow chart for the identification of clinical evidence



7.1.2 Efficacy

7.1.2.1 Study characteristics

Three[a] systematic reviews[17, 19, 20] and seven HTA reports[4, 5, 21-25] addressed the effectiveness of Trikafta® in comparison to standard of care. In total, these ten evidence synthesis reports included three different relevant RCTs,[29-31] which were also identified by our search. No additional relevant RCTs were found. The characteristics of the three included RCTs are summarized in Table 6. The

[a] The fourth identified systematic review only addressed safety (see part 7.1.3).

information about the primary and secondary endpoints was retrieved from the study protocols that are available in the trial registers. Some of these outcomes were not reported in the final publications.

The conclusions about the effectiveness of Trikafta® of the ten evidence synthesis reports are summarized in Table 7.

No RCTs were found comparing Trikafta® with standard of care in patients with genotypes F/F, F/RF or F/G.

Table 6: Study characteristics of the included RCTs

Characteristics	VX16-445-001 (Keating 2018)	VX17-445-102 (Middleton 2019)	VX19-445-116 (Mall 2022)
	Designs and populations		
Study design	Phase II, double-blind, parallel-group, placebo-controlled RCT	Phase III, double-blind, parallel-group, placebo-controlled RCT	Phase IIIb, double-blind, parallel-group, placebo-controlled RCT
Randomized (N)	F/MF: - ELX (50) -TEZ-IVA: N=10 - ELX (100) -TEZ-IVA: N=22 - ELX (200) -TEZ-IVA: N=21 - Triple placebo: N=12 F/F:* - ELX (200) -TEZ-IVA: N=21 - Placebo-TEZ-IVA: N=7	- ELX-TEZ-IVA: N=200 - Placebo: N=203	- ELX-TEZ-IVA: N=60 - Placebo: N=61
Inclusion criteria	- Age: 18+ - ppFEV1 ≥ 40% and ≤ 90% - 1 *F508del* mutation and 1 minimal function mutation (F/MF) or homozygous for *F508del* mutation (F/F)	- Age: 12+ - ppFEV1 ≥ 40% and ≤ 90% - 1 *F508del* mutation and 1 minimal function mutation (F/MF)	- Age: 6-11 years - ppFEV1 ≥ 70% - 1 *F508del* mutation and 1 minimal function mutation (F/MF)
	Drugs (relevant to the PICO question)		
Intervention	ELX 50-200 mg, TEZ 100 mg, and IVA 150 mg (every morning) plus IVA 150 mg (every evening)	ELX 200 mg, TEZ 100 mg, and IVA 150 mg (every morning) plus IVA 150 mg (every evening)	< 30 kg: ELX 100 mg, TEZ 50 mg, and IVA 75 mg (every morning) plus IVA 75 mg (every evening) ≥ 30 kg: ELX 200 mg, TEZ 100 mg, and IVA 150 mg (every

Characteristics	VX16-445-001 (Keating 2018)	VX17-445-102 (Middleton 2019)	VX19-445-116 (Mall 2022)
			morning) plus IVA 150 mg (every evening)
Comparator	Placebo	Placebo	Placebo
		Duration	
Follow-up duration	4 weeks	24 weeks	24 weeks
		Effectiveness outcomes	
Primary endpoint	Absolute change in $ppFEV_1$ from baseline through day 29	Absolute change in $ppFEV_1$ from baseline at week 4	Absolute change in $LCI_{2.5}$ from baseline through week 24
Secondary and other endpoints	- Absolute change in sweat chloride from baseline through day 29 - Relative change in $ppFEV_1$ from baseline through day 29 - Absolute change in CFQ-R respiratory domain score from baseline through day 29	- Absolute change in $ppFEV_1$ through week 24 - Number of pulmonary exacerbations, pulmonary exacerbations requiring IV antibiotics or hospitalization - Absolute change in sweat chloride at 4 weeks and through week 24 - Absolute change in CFQ-R respiratory domain score at 4 weeks and through week 24 - Absolute change in BMI, BMI z score, and weight at week 24 - Time to first pulmonary exacerbations, hospitalization for pulmonary exacerbations, IV antibiotics for pulmonary exacerbations - Duration of pulmonary exacerbations, hospitalization for pulmonary exacerbations, IV antibiotics for pulmonary exacerbations	- Absolute change in sweat chloride concentration from baseline through week 24 - Absolute change in $ppFEV_1$ from baseline through week 24 - Absolute change in CFQ-R respiratory domain score from baseline through week 24

Characteristics	VX16-445-001 (Keating 2018)	VX17-445-102 (Middleton 2019)	VX19-445-116 (Mall 2022)
		- Duration of hospitalization or IV antibiotics for pulmonary exacerbations - Absolute change in CFQ-R (non-RD) through week 24 - Absolute change in TSQM at 24 weeks - Planned hospitalizations - Unplanned hospitalizations - Duration of planned hospitalizations - Duration of unplanned hospitalizations	
Additional information			
Funding	Vertex Pharmaceuticals	Vertex Pharmaceuticals	Vertex Pharmaceuticals

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire–Revised; ELX-TEZ-IVA: elexacaftor-tezacaftor-ivacaftor; LCI: Lung Clearance Index; PICO: population, intervention, comparator, outcome; ppFEV1: percentage predicted forced expiratory volume in the first second; TSQM: Treatment Satisfaction Questionnaire for Medication.

* The comparator administered in the homozygous patients does not reflect the PICO inclusion criteria. Only the information for the 65 heterozygous patients which are compared with the relevant comparator are included in the study results of this report.

Study VX16-445-001 (NCT03227471)

In a phase 2 study, Keating et al. included 123 patients aged 18 years and older with cystic fibrosis who were homozygous for the *F508del* mutation (N=28) or who had the *F508del* mutation and a minimal function mutation (N=95), and with a percentage of predicted forced expiratory volume in the first second ($ppFEV_1$) between 40% and 90%.[29] The study had a complex design and compared the combination of elexacaftor (at 3 different doses: 50 mg, 100 mg, or 200 mg), tezacaftor and ivacaftor to triple placebo or to the combination of placebo, tezacaftor and ivacaftor. From the 123 included patients, 65 heterozygous patients underwent randomization to the comparison of interest: the combination of elexacaftor once daily (at 3 different doses: 50 mg [N=10], 100 mg [N=22], 200 mg [N=21]), tezacaftor 100 mg once daily, and ivacaftor 150 mg every 12 hours on the one hand, vs. triple placebo (N=12) on the other hand. Clinical efficacy was evaluated on the basis of the absolute and relative change in $ppFEV_1$ from baseline through day 29, the absolute change in sweat chloride from baseline through day 29 and the absolute change in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score from baseline through day 29. Of the included

patients, 40% were females. Mean baseline ppFEV$_1$ was 56.4%, 60.0% and 59.4% in the three intervention groups vs. 59.0% in the placebo group.

In the safety analysis, a total of 74 patients receiving Trikafta® were included, including 21 patients homozygous for the *F508del* mutation who received Trikafta® as part of the comparison with Symdeko®.

Study VX17-445-102 (NCT03525444)

Middleton et al. included 403 patients aged 12 years and older with cystic fibrosis who had the *F508del* mutation and a minimal function mutation, and with a ppFEV$_1$ between 40% and 90%.[31] The patients were randomized to Trikafta® (elexacaftor at a dose of 200 mg once daily) (N=200) or identical placebo (N=203) for 24 weeks. Randomization was stratified for age at screening (<18 years vs. ≥18 years). The primary outcome was the absolute change in ppFEV1 at 4 weeks. Key secondary end points were the absolute change in ppFEV1 through week 24, number of pulmonary exacerbations through week 24, absolute change in sweat chloride concentration through week 24, absolute change in the CFQ-R respiratory domain score through week 24, absolute change in body mass index (BMI) at week 24, absolute change in sweat chloride concentration at week 4, and absolute change from baseline in the CFQ-R respiratory domain score at week 4. Of the included patients, 48.1% were females and 71.2% were adults. Mean baseline ppFEV$_1$ was 61.6% in the intervention group vs. 61.3% in the placebo group.

Study VX19-445-116 (NCT04353817)

Mall et al. included 121 children aged 6 to 11 years with cystic fibrosis who had the *F508del* mutation and a minimal function mutation, and with a ppFEV$_1$ of at least 70%.[30] The patients were randomized to Trikafta® (N=60) or placebo (N=61) for 24 weeks. Dosing was based on weight at screening: children weighing <30 kg received elexacaftor 100 mg once daily, tezacaftor 50 mg once daily, and ivacaftor 75 mg every 12 hours (50% of adult dose), whereas children weighing ≥30 kg received elexacaftor 200 mg once daily, tezacaftor 100 mg once daily, and ivacaftor 150 mg every 12 hours (full adult dose). The primary endpoint was absolute change in lung clearance index$_{2.5}$ (LCI$_{2.5}$) from baseline through week 24. Secondary endpoints were absolute change in sweat chloride concentration from baseline through week 24 and safety and tolerability. Additional efficacy endpoints included absolute changes in ppFEV$_1$ and CFQ-R respiratory domain score from baseline through week 24. Of the included patients, 58% were females. At baseline, 60.0% of the children in the intervention group had a ppFEV$_1$ >90%, vs. 45.9% in the placebo group.

Table 7: Summary of the ten included evidence synthesis reports

Study / report	Type	Search date	Included RCTs			Conclusions regarding effectiveness
			VX16-445-001	VX17-445-102	VX19-445-116	
Bailey 2021[17]	SR	May 2018 (Update until February 2020)	(not mentioned)	x	(published after search date)	The efficacy of CFTR modulators on improving nutritional status in individuals with CF was highly dependent on the therapy formulation (single vs. combination therapy) and the CFTR mutation of the targeted population. As new, highly effective CFTR modulators are developed, the potential for improvement in growth and nutrition status coupled with increasing longevity presents new challenges and opportunities for interdisciplinary teamwork and partnership in nutrition care for people with CF. Expanding the body of research on how specific CFTR modulators affect nutrition status, and on best clinical practice to adapt to these effects is necessary to determine optimal nutritional strategies in this population, and will allow for improved care of people with CF as they age.
Southern 2020[19]	SR + MA	October 2020	x	x		There is high-quality evidence of clinical efficacy […] for triple (elexacaftor-tezacaftor-ivacaftor) therapy in people with CF with one or two *F508del* variants aged 12 years or older. Further RCTs are required in children (under 12 years) and those with more severe respiratory function.
Wang 2022[20]	SR + MA	December 2021	x	x	(published after search date)	The triple therapy combination had highly significant efficacy … in treating CF, as compared with placebo or active control, for patients with F/F, F/MF, F/RF or F-gating mutations. More well-designed RCTs are needed to support the efficacy and safety, and extend the indications for younger patients diagnosed with CF, to achieve radical treatment for CF before the development of the disease.
CADTH 2021[21]	HTA	June 2021	excluded	x	(out of scope)	A 24-week, placebo-controlled, RCT (Study 102, N = 403) conducted in patients with an F/MF genotype demonstrated that, compared with placebo, 24-weeks of treatment with ELX-TEZ-IVA

Study / report	Type	Search date	Included RCTs			Conclusions regarding effectiveness
			VX16-445-001	VX17-445-102	VX19-445-116	
						was associated with statistically significant and clinically meaningful improvements in lung function (increase in ppFEV1), nutritional status (increase in BMI), health-related quality of life (increase in CFQ-R [RD] scores), CF biomarkers (reduction in sweat chloride), and a reduced rate of pulmonary exacerbations, including events that required IV antibiotics and/or hospitalization to manage. … Patients with advanced lung disease were largely excluded from the phase III RCTs; however, post hoc subgroup analyses and data from 2 short-term observational studies suggest that treatment with ELX-TEZ-IVA resulted in clinically meaningful improvements in lung function in these patients.
CADTH 2022[4]	HTA	June 2021	(excluded in CADTH 2021)	(included in CADTH 2021)	x	For patients 6 to 11 years of age, a 24-week, double-blind, placebo-controlled RCT (Study 116; N = 121) and a pivotal, single-arm, open-label trial (Study 106B; N = 66) demonstrated that treatment with ELX-TEZ-IVA resulted in clinically meaningful improvements in lung function (increase in ppFEV1), nutritional status (increase in BMI z scores), and HRQoL (increase in CFQ-R respiratory domain scores) and CF biomarkers (reduction in sweat chloride). In addition, AE data suggested that ELX-TEZ-IVA reduced the occurrence of pulmonary exacerbations in pediatric patients. The clinical studies for ELX-TEZ-IVA were limited to patients with an F/MF (Study 116 and Study 106B) or F/F genotype. As Study 106B was a single-arm trial, the sponsor conducted an indirect comparison to derive estimates for the comparative efficacy of ELX-TEZ-IVA versus placebo, LUM-IVA, and TEZ-IVA. No clinical studies were conducted on ELX-TEZ-IVA in pediatric patients with F/RF or F/G genotypes; however, the clinical experts noted that ELX-TEZ-IVA would result in clinically meaningful improvements for these patients, based on the evidence reported for ELX-TEZ-IVA in adult patients with F/RF and F/G genotypes and the results in pediatric studies of patients with F/F and F/MF genotypes. This is consistent with the input

Study / report	Type	Search date	Included RCTs			Conclusions regarding effectiveness
			VX16-445-001	VX17-445-102	VX19-445-116	
						from patient and clinician groups who have indicated all patients with at least 1 *F508del* mutation are likely to benefit from treatment with ELX-TEZ-IVA.
GBA 2022[22]	HTA	November 2021	(out of scope)	(out of scope)	x	In summary, taking all patient-relevant effects into account, their strength and relevance as well as the evidence for the overall collective ivacaftor/tezacaftor/elexacaftor (plus ivacaftor) in the entire indication A (*patients with CF from 6 to 11 years who are heterozygous for the F508del-mutation in the CFTR gene and have a minimal function (MF) mutation on the second allele*) compared to the appropriate comparator “best supportive care”, an indication of a significant additional benefit was found.
ICER 2020[5]	HTA (incl. NMA)	November 2019	x	x	(published after search date)	**Trikafta® for Patients who are Homozygous for the F508del Mutation:** Given that Trikafta® is Symdeko® plus an additional modulator, the consistent evidence in controlled trials of lung function improvement, with clinically significant improvements and associated reductions in acute pulmonary exacerbations, and with no evidence of significant harms, we have high certainty Trikafta® provides a substantial (moderate-large) net health benefit relative to best supportive care and to Symdeko®. We therefore assign a rating of “superior” (A) to the comparative clinical effectiveness of Trikafta® in this population, both versus best supportive care and versus Symdeko®. **Trikafta for Patients who are Heterozygous for the F508del Mutation and a Residual Function Mutation:** There are no published randomized trial or observational data for Trikafta® in this population. However, because Trikafta® is Symdeko® plus an additional CFTR modulator drug it should be at least as effective unless there are interactions that decrease the effectiveness of Symdeko®.

Study / report	Type	Search date	Included RCTs			Conclusions regarding effectiveness
			VX16-445-001	VX17-445-102	VX19-445-116	
						In the population of patients homozygous for the F508del mutation, Trikafta® was significantly more effective than Symdeko® and there was no evidence of additional toxicity with Trikafta®. Thus, we judge that Trikafta® will be at least as effective as Symdeko® versus best supportive care (B+). Using similar logic, we judge that we have moderate certainty that Trikafta® has a comparable, small or substantial net heath benefit compared with Symdeko®, with high certainty of at least a comparable net health benefit (C++). **Trikafta® for Patients who are Heterozygous for the f508del Mutation With a Minimal Function Mutation:** The single 24-week randomized controlled trial of Trikafta® in this population demonstrated clinically significant improvements in lung function improvement and respiratory quality of life, with clinically significant improvements and associated reductions in acute pulmonary exacerbations, and no evidence of significant harms. Thus, we have high certainty Trikafta® provides a substantial (moderate-large) net health benefit relative to best supportive care. We therefore assign a rating of “superior” (A) to the comparative clinical effectiveness of Trikafta® in this population.
IQWIG 2022[23]	HTA	November 2021	(out of scope)	(out of scope)	x	All things considered, exclusively favourable effects of ivacaftor/tezacaftor/elexacaftor + ivacaftor were found in comparison with BSC. There is a hint of considerable added benefit for the outcome of pulmonary exacerbations, while a hint of lesser harm of the same extent is found for the outcome of abdominal pain. In summary, this results in a hint of considerable added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the appropriate comparator therapy of BSC for CF patients 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation.

Study / report	Type	Search date	Included RCTs			Conclusions regarding effectiveness
			VX16-445-001	VX17-445-102	VX19-445-116	
ZIN 2021[24]	HTA	December 2020	excluded	x	(out of scope)	In studies up to 24 weeks, elexacaftor/tezacaftor/ivacaftor with ivacaftor has been shown to provide an improvement in long-term function, a reduction in the number of pulmonary exacerbations and a reduction in respiratory symptoms in patients aged 12 years or over with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and have an additional mutation in the CFTR gene with a minimal function of the CFTR.
ZIN 2022[25]	HTA	January 2021	excluded	x	(out of scope)	For the treatment of CF patients ≥ 12 years old with at least one F508del mutation in the CFTR gene, elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor are preferred above other CFTR regulators and standard symptomatic treatment. For other indications, other CFTR regulators (lumacaftor/ivacaftor, tezacaftor/ivacaftor in combination with ivacaftor and ivacaftor monotherapy) can be prescribed for indications for which they are registered. There is still a lot of uncertainty about the long-term effectiveness and safety of CFTR regulators. To stimulate the appropriate use of CFTR regulators it is recommended to evaluate the treatment on a regular basis using the stop criteria that are included in the quality standard of cystic fibrosis.

BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire–Revised; CFTR: Cystic fibrosis transmembrane conductance regulator; ELX-TEZ-IVA: elexacaftor-tezacaftor-ivacaftor; HRQoL: health-related quality of life; HTA: health Technology Assessment; LUM-IVA: lumacaftor-ivacaftor; MA: meta-analysis: ppFEV1: percentage predicted forced expiratory volume in the first second; RCT: randomized controlled trial; SR: systematic review; TEZ-IVA: tezacaftor-ivacaftor.

Bailey et al.[17] conducted a systematic review (without meta-analysis) to determine the effects of various CFTR modulator therapies, compared to placebo/control, on anthropometric and body composition parameters in children and adults with cystic fibrosis. They included one of the three relevant RCTs.[31]

In a Cochrane review with a broad scope, Southern et al.[19] included 19 RCTs that evaluated the effectiveness and safety of corrector therapies for people with cystic fibrosis with class II CFTR gene variants (including *F508del*). Two of the three relevant RCTs were included,[29, 31] and a meta-analysis of these two RCTs was performed for some outcomes.

Wang et al.[20] conducted a systematic review about the efficacy and safety of triple combination therapy according to different genotypes and comparators. Two of the three relevant RCTs were included.[29, 31] They also performed a meta-analysis, but mixed studies with various types of triple combination therapy (i.e. also VX-659 instead of elexacaftor) and/or comparators (i.e. active treatment instead of placebo), making the meta-analysis irrelevant for our report.

CADTH (Canadian Agency for Drugs & Technologies in Health) conducted two separate systematic reviews about the efficacy and safety of Trikafta®, one specifically focused on patients aged ≥ 12 years[21] and one extending the inclusion criteria to patients aged ≥ 6 years.[4] The first review included study VX17-445-102,[31] while the second review included study VX19-445-116.[30] The study of Keating et al.[29] was excluded because of study design (phase 2). A meta-analysis was not performed.

GBA (Gemeinsamer Bundesausschuss – Federal Joint Committee) published an extensive HTA report about Trikafta® treatment of children aged 6-11 years with cystic fibrosis who are heterozygous for the *F508del* mutation and with a minimal function mutation in the CFTR gene.[22] They included study VX19-445-116.[30] A meta-analysis was not performed.

For their HTA report, ICER (Institute for Clinical and Economic Review) performed a systematic review of Trikafta®, but also updated a prior review of Kalydeco®, Orkambi® and Symdeko®.[5] They included two of the three relevant RCTs.[29, 31] In addition, they performed a network meta-analysis (NMA) for patients who are homozygous for the *F508del* mutation. For this NMA, ICER combined the results of study VX17-445-103 (comparing Trikafta® with Symdeko®)[34] and study VX14-661-106 (comparing Symdeko® with placebo).[58]

IQWIG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) published an HTA report about Trikafta® treatment of children aged 6-11 years with cystic fibrosis who are heterozygous for the *F508del* mutation and with a minimal function mutation in the CFTR gene.[23] They included study VX19-445-116.[30] A meta-analysis was not performed.

ZIN (Zorginstituut Nederland) conducted a systematic review about the efficacy and safety of Trikafta® in patients aged ≥ 12 years who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and with a minimal function mutation in the CFTR gene.[24]

In a second systematic review they extended their scope to additional genotypes (F/G, F/RF and F/N).[25] They included study VX17-445-102.[31] The study of Keating et al.[29] was excluded because of study design (phase 2). A meta-analysis was not performed.

7.1.2.2 Study quality appraisal

All three RCTs were of good methodological quality (Table 8). They all used an interactive web response system to randomize and allocate the participants. According to the study protocols available through clinicaltrials.gov, all subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team were blinded to the treatment codes. Furthermore, the three trials included all randomized patients in the analyses (intention-to-treat analysis). The trials were sponsored by Vertex Pharmaceuticals.

Table 8: Risk of bias of included RCTs

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Keating 2018	Low	Low	Low	Low	Low	Low	Unclear
Middleton 2019	Low	Low	Low	Low	Low	Low	Unclear
Mall 2022	Low	Low	Low	Low	Low	Low	Unclear

RCT: randomized controlled trial.

7.1.2.3 Results

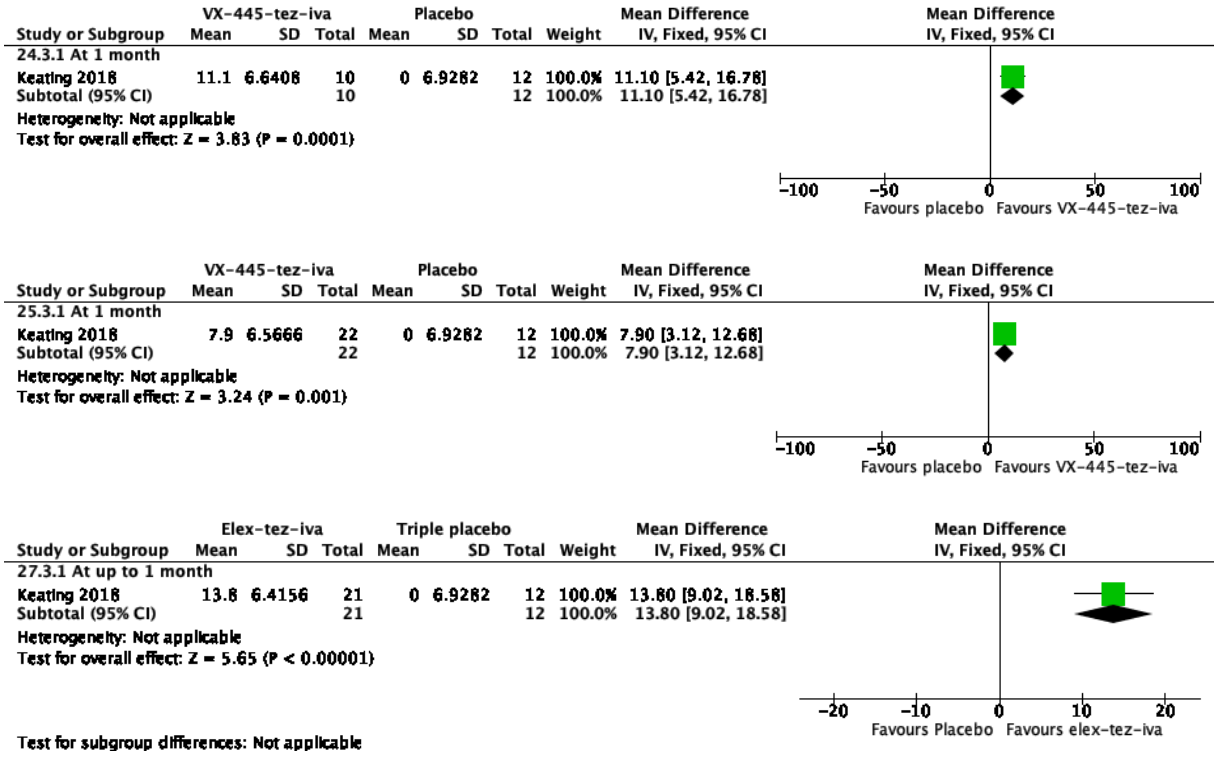
An overview of the reported efficacy outcomes is presented in Table 9 (RCTs) and in Table 10 (meta-analyses). A more detailed discussion is provided below.

7.1.2.3.1 Percentage of predicted FEV_1

Study VX16-445-001 (NCT03227471)

Keating et al. reported an absolute change from baseline in $ppFEV_1$ at day 29 (mean +/- standard error) of 0.0 +/- 2.0 for triple placebo, 11.1 +/- 2.1 for elexacaftor 50 mg, 7.9 +/- 1.4 for elexacaftor 100 mg, and 13.8 +/- 1.4 for elexacaftor 200 mg, respectively.[29] P-values were not reported by the authors, but input of the data in Review Manager 5.3 confirmed the statistical significance of the effect of elexacaftor (all 3 doses) compared to triple placebo (Figure 2).

Figure 2: Forest plots of absolute change from baseline in ppFEV1 reported in study VX16-445-001



ppFEV1: percentage predicted forced expiratory volume in the first second

Study VX17-445-102 (NCT03525444)

Middleton et al.[31] reported an absolute change from baseline in $ppFEV_1$ at 4 weeks (mean [95%CI]) of -0.2 (-1.3 to 1.0) in the placebo group versus 13.6 (12.4 to 14.8) in the Trikafta® group. The between-group mean difference was 13.8 (12.1 to 15.4; p<0.001). Subgroup analysis showed that the mean treatment difference was consistent across the two predefined age groups (12-18 years: 13.8 [10.0 to 17.5]; ≥18 years: 13.6 [11.9 to 15.4]).

Through week 24, the absolute change from baseline in $ppFEV_1$ was -0.4 (-1.5 to 0.7) in the placebo group versus 13.9 (12.8 to 15.0) in the Trikafta® group. The between-group mean difference was 14.3 (12.7 to 15.8; p<0.001). No subgroup analysis was reported for this timepoint.

Study VX19-445-116 (NCT04353817)

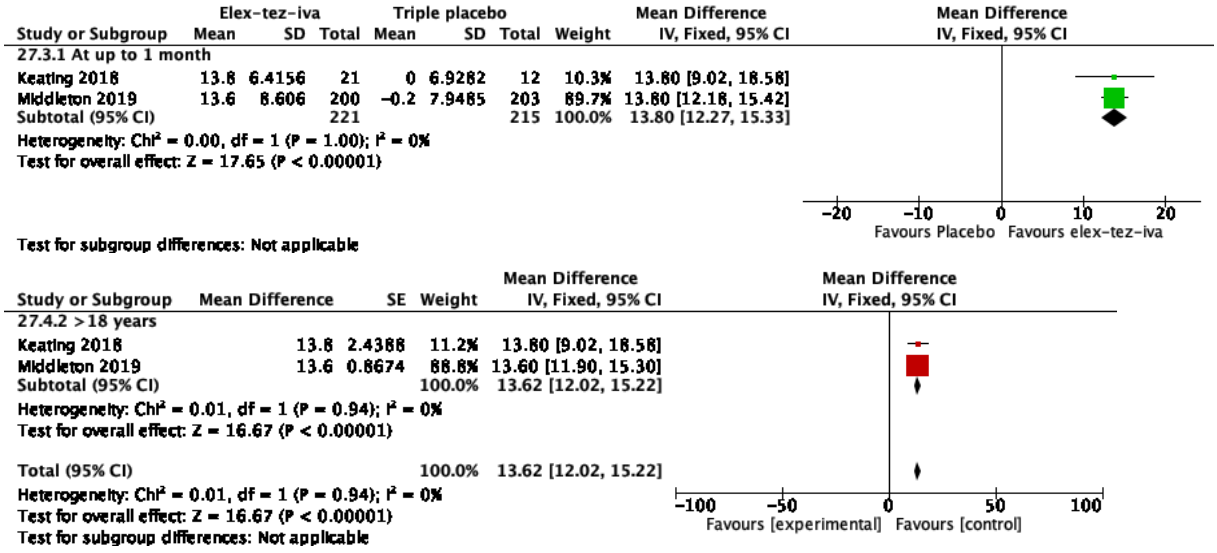
Mall et al.[30] reported an absolute change from baseline in $ppFEV_1$ through week 24 (mean [95%CI]) of -1.5 (-4.4 to 1.4) in the placebo group versus 9.5 (6.6 to 12.4) in the Trikafta® group. The between-group mean difference was 11.0 (6.9 to 15.1; p<0.0001).

Additional information from evidence syntheses

ICER performed a network meta-analysis (NMA) comparing three cystic fibrosis modulator therapies (Orkambi®, Symdeko® and Trikafta®) with placebo in patients homozygous for the *F508del* mutation.[5] The absolute change in $ppFEV_1$ was significantly higher with Trikafta® than with placebo (14.0%, 95%CI 11.3 to 16.7).

We combined the data of study VX16-445-001 and study VX17-445-102 (Table 10). A significant effect was found in favour of Trikafta® up to 1 month (mean difference 13.8, 95%CI 12.27 to 15.33). When only the subgroup of 18+ was considered, the effect slightly changed (mean difference 13.62, 95%CI 12.02 to 15.22) (Figure 3).

Figure 3: Pooled effect on absolute change from baseline in ppFEV1 (1st figure: 12+; 2nd figure: 18+)



ppFEV1: percentage predicted forced expiratory volume in the first second

7.1.2.3.2 Lung clearance index

Study VX16-445-001 (NCT03227471)

Keating et al. did not report the effect of Trikafta® on LCI.

Study VX17-445-102 (NCT03525444)

Middleton et al. did not report the effect of Trikafta® on LCI.

Study VX19-445-116 (NCT04353817)

Mall et al.[30] reported an absolute change from baseline in $LCI_{2.5}$ through week 24 (mean [95%CI]) of -0.02 (-0.34 to 0.29) in the placebo group versus -2.29 (-2.60 to -1.97) in the Trikafta® group. The between-group mean difference was -2.26 (-2.71 to -1.81; p<0.0001).

7.1.2.3.3 Pulmonary exacerbations

Study VX16-445-001 (NCT03227471)

Keating et al. did not report the effect of Trikafta® on pulmonary exacerbations.

Study VX17-445-102 (NCT03525444)

Middleton et al.[31] reported 113 pulmonary exacerbations through week 24 (annualized estimated event rate: 0.98) in the placebo group versus 41 pulmonary exacerbations (annualized estimated

event rate: 0.37) in the Trikafta® group. The rate ratio was 0.37 (95%CI 0.25 to 0.55; p<0.001). No subgroup analysis was reported for this outcome.

A similar benefit was seen with respect to the rate of exacerbations that led to hospitalization (rate ratio 0.29; 95%CI 0.14 to 0.61) or that were treated with intravenous antibiotics (rate ratio 0.22; 95%CI 0.11 to 0.43). A higher percentage of patients in the Trikafta® group than in the placebo group remained free of pulmonary exacerbations.

The time-to-first pulmonary exacerbation was significantly longer in the Trikafta® group than in the placebo group (hazard ratio 0.34; 95%CI 0.22 to 0.52).

Study VX19-445-116 (NCT04353817)

Mall et al. did not report the effect of Trikafta® on pulmonary exacerbations.

7.1.2.3.4 Body mass index / weight

Study VX16-445-001 (NCT03227471)

Keating et al. did not report the effect of Trikafta® on BMI or weight.

Study VX17-445-102 (NCT03525444)

Middleton et al.[31] reported an absolute change from baseline in BMI at 24 weeks (mean [95%CI]) of 0.09 (-0.05 to 0.22) in the placebo group versus 1.13 (0.99 to 1.26) in the Trikafta® group. The between-group mean difference was 1.04 (0.85 to 1.23; p<0.001). No subgroup analysis was reported for this outcome.

The absolute change from baseline in body mass index-for-age z score at 24 weeks was significantly higher in the Trikafta® group than in the placebo group (mean difference 0.30; 95%CI 0.17 to 0.43). The absolute change from baseline in body weight (kg) from baseline at 24 weeks was also significantly higher in the Trikafta® group than in the placebo group (mean difference 2.9; 95%CI 2.3 to 3.4).

Study VX19-445-116 (NCT04353817)

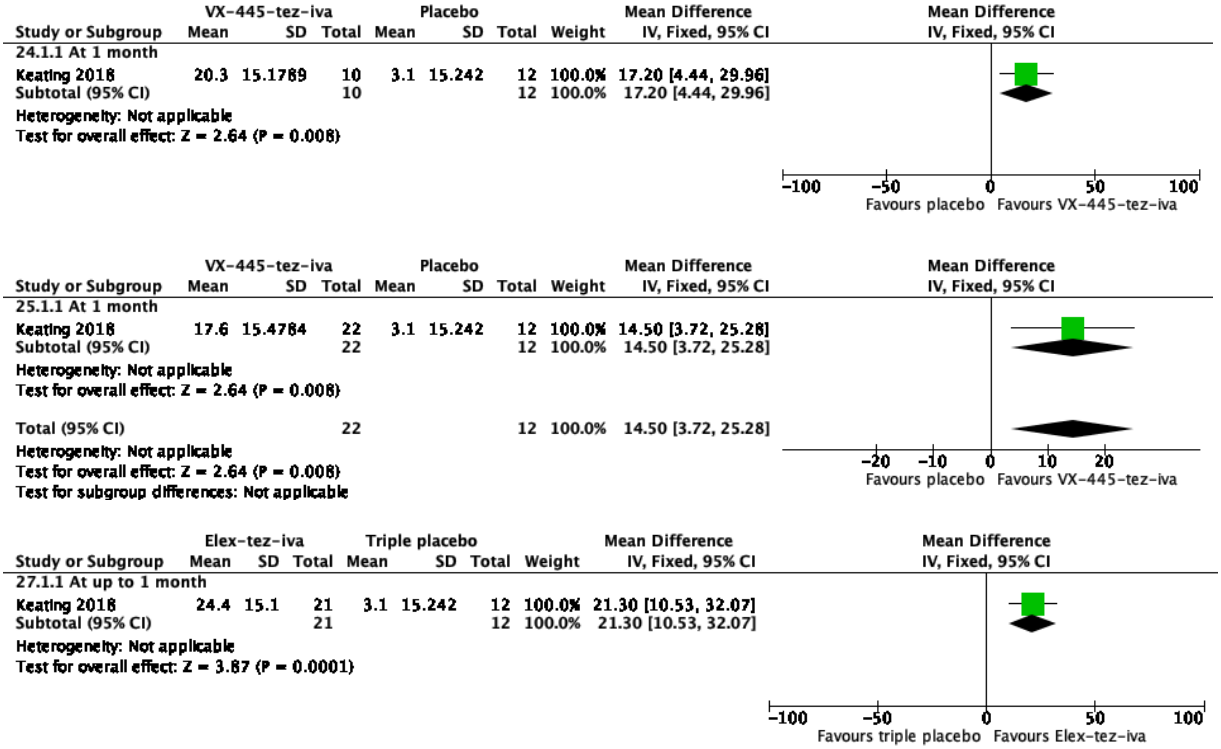
Mall et al. did not report the effect of Trikafta® on BMI or weight.

7.1.2.3.5 Health-related quality of life

Study VX16-445-001 (NCT03227471)

Keating et al.[29] reported an absolute change from baseline in CFQ-R respiratory domain score at day 29 (mean +/- standard error) of 3.1 +/- 4.4 points for triple placebo, 20.3 +/- 4.8 points for elexacaftor 50 mg, 17.6 +/- 3.3 points for elexacaftor 100 mg, and 24.4 +/- 3.3 points for elexacaftor 200 mg, respectively. P-values were not reported by the authors, but input of the data in Review Manager 5.3 confirmed the statistical significance of the effect of elexacaftor (all 3 doses) compared to triple placebo (Figure 4).

Figure 4: Forest plots of absolute change from baseline in CFQ-R respiratory domain score reported in study VX16-445-001



CFQ-R: Cystic Fibrosis Questionnaire–Revised

Study VX17-445-102 (NCT03525444)

Middleton et al.[31] reported an absolute change from baseline in CFQ-R respiratory domain score at 24 weeks (mean [95%CI]) of -2.7 points (-4.6 to -0.8) in the placebo group versus 17.5 points (15.6 to 19.5) in the Trikafta® group. The between-group mean difference was 20.2 points (17.5 to 23.0; p<0.001).

At 4 weeks, the absolute change from baseline in CFQ-R respiratory domain score was -1.9 points (-4.2 to 0.3) in the placebo group versus 18.1 points (15.9 to 20.4) in the Trikafta® group.[31] The between-group mean difference was 20.1 points (16.9 to 23.2; p<0.001).

No subgroup analysis was reported for this outcome.

Study VX19-445-116 (NCT04353817)

Mall et al.[30] reported an absolute change from baseline in CFQ-R respiratory domain score through week 24 (mean [95%CI]) of 0.5 points (-2.7 to 3.6) in the placebo group versus 5.9 points (2.8 to 9.1) in the Trikafta® group. The between-group mean difference was 5.5 points (1.1 to 10.0; p=0.0174).

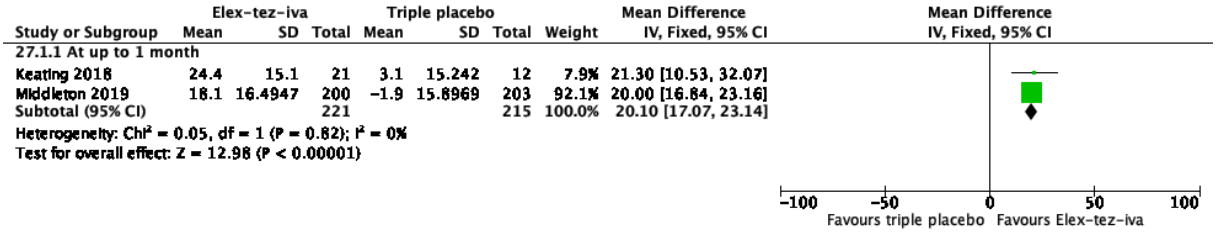
Additional information from evidence syntheses

ICER performed a network meta-analysis (NMA) comparing three cystic fibrosis modulator therapies (Orkambi®, Symdeko® and Trikafta®) with placebo in patients homozygous for the *F508del*

mutation.[5] The absolute change in CFQ-R respiratory domain score was significantly higher with Trikafta® than with placebo (22.5 points, 95%CI 16.6 to 28.4).

Southern et al.[19] pooled the results from study VX16-445-001 and study VX17-445-102. Trikafta® (with elexacaftor at a dosage of 200 mg once daily) had a significant effect on the CFQ-R respiratory domain score compared with placebo at 1 month (change from baseline, mean difference 19.15 points, 95%CI 16.12 to 22.19). However, the wrong data were used for the placebo group in study VX16-445-001. We repeated the meta-analysis using the correct data and found a stronger pooled effect (mean difference 20.1 points, 95%CI 17.07 to 23.14) (Figure 5).

Figure 5: Pooled effect on absolute change from baseline in CFQ-R respiratory domain score (corrected data of Southern 2020)



CFQ-R: Cystic Fibrosis Questionnaire–Revised

7.1.2.3.6 Sweat chloride

Study VX16-445-001 (NCT03227471)

Keating et al.[29] reported an absolute change from baseline in sweat chloride at day 29 (mean +/- standard error) of -2.2 +/- 3.9 mmol/l for triple placebo, -38.2 +/- 4.2 mmol/l for elexacaftor 50 mg, -33.2 +/- 2.8 mmol/l for elexacaftor 100 mg, and -39.1 +/- 2.9 mmol/l for elexacaftor 200 mg, respectively. The p-value for decreasing dose-response trend was ≤0.0001.

Study VX17-445-102 (NCT03525444)

Middleton et al.[31] reported an absolute change from baseline in sweat chloride at 24 weeks (mean [95%CI]) of -0.4 mmol/l (-2.2 to 1.4) in the placebo group versus -42.2 mmol/l (-44.0 to -40.4) in the Trikafta® group. The between-group mean difference was -41.8 mmol/l (-44.4 to -39.3; p<0.001).

At 4 weeks, the absolute change from baseline in sweat chloride was 0.1 mmol/l (-1.9 to 2.0) in the placebo group versus -41.2 mmol/l (-43.1 to -39.2) in the Trikafta® group.[31] The between-group mean difference was -41.2 mmol/l (-44.0 to -38.5; p<0.001).

No subgroup analysis was reported for this outcome.

Study VX19-445-116 (NCT04353817)

Mall et al.[30] reported an absolute change from baseline in sweat chloride through week 24 (mean [95%CI]) of -0.9 mmol/l (-3.8 to 2.0) in the placebo group versus -52.1 mmol/l (-55.0 to -49.2) in the Trikafta® group. The between-group mean difference was -51.2 mmol/l (-55.3 to -47.1; p<0.0001).

Additional information from evidence syntheses

ICER performed a network meta-analysis (NMA) comparing three cystic fibrosis modulator therapies (Orkambi®, Symdeko® and Trikafta®) with placebo in patients homozygous for the *F508del* mutation.[5] The absolute change in sweat chloride was significantly higher with Trikafta® than with placebo (-55.2 mmol/l, 95%CI -60.4 to -50.0).

Southern et al.[19] pooled the results from study VX16-445-001 and study VX17-445-102. Trikafta® (with elexacaftor at a dosage of 200 mg once daily) had a significant effect on sweat chloride compared with placebo at 1 month (absolute change from baseline, mean difference -41.80 mmol/l, 95%CI -43.60 to -38.33).

Table 9: Efficacy outcomes by genotype and/or age: individual RCTs

Study	Daily dosage	Outcome	Time point	Effect estimate	Study type	GRADE
Genotype: heterozygous, with *F508del* mutation and a minimal function mutation						
Age: 6-11 years						
Mall 2022	ELX 100-200 mg	ppFEV1	24 weeks	MD 11.0 (95%CI 6.9 to 15.1)	RCT	High
Mall 2022	ELX 100-200 mg	$LCI_{2.5}$	24 weeks	MD -2.26 (95%CI -2.71 to -1.81)	RCT	High
Mall 2022	ELX 100-200 mg	CFQ-R	24 weeks	MD 5.5 (95%CI 1.1 to 10.0)	RCT	High
Mall 2022	ELX 100-200 mg	Sweat chloride	24 weeks	MD -51.2 (95%CI -55.3 to -47.1)	RCT	High
Age: 12+ years						
Middleton 2019	ELX 200 mg	ppFEV1	4 weeks	MD 13.8 (12.1 to 15.4)	RCT	High
Middleton 2019	ELX 200 mg	ppFEV1	24 weeks	MD 14.3 (12.7 to 15.8)	RCT	High
Middleton 2019	ELX 200 mg	Pulmonary exacerbations	24 weeks	RR 0.37 (0.25 to 0.55)	RCT	High
Middleton 2019	ELX 200 mg	BMI	24 weeks	MD 1.04 (0.85 to 1.23)	RCT	High
Middleton 2019	ELX 200 mg	CFQ-R	4 weeks	MD 20.1 (16.9 to 23.2)	RCT	High
Middleton 2019	ELX 200 mg	CFQ-R	24 weeks	MD 20.2 (17.5 to 23.0)	RCT	High
Middleton 2019	ELX 200 mg	Sweat chloride	4 weeks	MD -41.2 (-44.0 to -38.5)	RCT	High
Middleton 2019	ELX 200 mg	Sweat chloride	24 weeks	MD -41.8 (-44.4 to -39.3)	RCT	High

Study	Daily dosage	Outcome	Time point	Effect estimate	Study type	GRADE
Age: 12-18 years						
Middleton 2019	ELX 200 mg	ppFEV1	4 weeks	MD 13.8 (10.0 to 17.5)	RCT (subgroup)	High
Age: 18+ years						
Keating 2018	ELX 50 mg	ppFEV1	Day 29	MD 11.1 (5.42 to 16.78)	RCT	High
Keating 2018	ELX 100 mg	ppFEV1	Day 29	MD 7.9 (3.12 to 12.68)	RCT	High
Keating 2018	ELX 200 mg	ppFEV1	Day 29	MD 13.8 (9.02 to 18.58)	RCT	High
Middleton 2019	ELX 200 mg	ppFEV1	4 weeks	MD 13.6 (11.9 to 15.4)	RCT (subgroup)	High
Keating 2018	ELX 50 mg	CFQ-R	Day 29	MD 17.2 (4.44 to 29.96)	RCT	High
Keating 2018	ELX 100 mg	CFQ-R	Day 29	MD 14.5 (3.72 to 25.28)	RCT	High
Keating 2018	ELX 200 mg	CFQ-R	Day 29	MD 21.3 (10.53 to 32.07)	RCT	High
Keating 2018	ELX 50 mg	Sweat chloride	Day 29	MD -36.0 (-47.23 to -24.77)	RCT	High
Keating 2018	ELX 100 mg	Sweat chloride	Day 29	MD -31.0 (-40.41 to -21.59)	RCT	High
Keating 2018	ELX 200 mg	Sweat chloride	Day 29	MD -36.9 (-46.43 to -27.37)	RCT	High

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire–Revised; ELX: elexacaftor; GRADE: Grading of Recommendations, Assessment, Development and Evaluations; LCI: Lung Clearance Index; MD: mean difference; ppFEV1: percentage predicted forced expiratory volume in the first second; RCT: randomized controlled trial.

Table 10: Efficacy outcomes by genotype and/or age: meta-analyses

Study	Daily dosage	Outcome	Time point	Effect estimate	Study type	GRADE
Genotype: heterozygous, with *F508del* mutation and a minimal function mutation						
Age: 12+ years						
Own meta-analysis	ELX 200 mg	ppFEV1	1 month	MD 13.8 (12.27 to 15.33)	Meta-analysis	High
Own meta-analysis	ELX 200 mg	CFQ-R	1 month	MD 20.1 (17.07 to 23.14)	Meta-analysis	High
Southern 2020	ELX 200 mg	Sweat chloride	1 month	MD -40.96 (-43.60 to -38.33)	Meta-analysis	High
Age: 18+ years						
Own meta-analysis	ELX 200 mg	ppFEV1	1 month	MD 13.62 (12.02 to 15.22)	Meta-analysis	High
Genotype: homozygous for *F508del* mutation						
ICER 2020	ELX 200 mg	ppFEV1	24 weeks	MD 14.0 (11.3 to 16.7)	NMA	High
ICER 2020	ELX 200 mg	CFQ-R	24 weeks	MD 22.5 (16.6 to 28.4)	NMA	High
ICER 2020	ELX 200 mg	Sweat chloride	24 weeks	MD -55.2 (-60.4 to -50.0)	NMA	High

CFQ-R: Cystic Fibrosis Questionnaire–Revised; ELX: elexacaftor; GRADE: Grading of Recommendations, Assessment, Development and Evaluations; MD: mean difference; NMA: network meta-analysis; ppFEV1: percentage predicted forced expiratory volume in the first second; RR: rate ratio.

7.1.3 Safety

7.1.3.1 Study characteristics

The three RCTs that were included for the efficacy analysis also reported on the safety of Trikafta®. In addition, three other RCTs (comparing Trikafta® with an active control) and 22 single-arm studies provided primary information on the safety of Trikafta®.[36-57] Furthermore, four systematic reviews[17-20] and 7 HTA reports[4, 5, 21-25] also reported on safety.

7.1.3.2 Trikafta® vs. placebo (RCTs)

Study VX16-445-001 (NCT03227471)

Keating et al.[29] reported at least one adverse event in 92% of the patients who received Trikafta® vs. 100% of the patients who received triple placebo. Among the patients who received Trikafta® and had an adverse event, 53% had mild events, 43% had moderate events, and 4% had severe events. Serious adverse events occurred in 4% of the patients who received Trikafta® vs. 17% of the patients who received triple placebo. The serious adverse events in the patients who received Trikafta® comprised two events of infective pulmonary exacerbation of cystic fibrosis, two events of distal intestinal obstruction syndrome, and one event of jugular venous thrombosis. No deaths occurred during the trial. Three patients (4%) in the Trikafta® group discontinued treatment because of adverse events. Adverse events leading to discontinuation in patients receiving Trikafta® included rash, elevated bilirubin level, and chest pain. Administration of Trikafta® was interrupted in 3 patients (4%) owing to adverse events, which included elevated levels of aspartate aminotransferase, alanine aminotransferase, and creatine kinase in addition to myopathy (all in the same patient) and an elevated bilirubin level and constipation (each of which occurred in a different patient).

The most common adverse events (i.e. incidence >10%) that occurred in patients receiving Trikafta® were cough (31%), increased sputum production (27%), infective pulmonary exacerbation of cystic fibrosis (20%), hemoptysis (14%), and pyrexia (12%). The incidence of abnormal results on tests of liver function, defined as a result greater than three times the upper limit of the normal range for levels of aspartate aminotransferase or alanine aminotransferase, was 8%. The incidence of elevation of bilirubin levels greater than two times the upper limit of normal was 3%.

In their Cochrane review, Southern et al.[19] provided statistical comparisons between the different doses of elexacaftor and triple placebo; none of the differences were statistically significant.

Study VX17-445-102 (NCT03525444)

Middleton et al.[31] reported at least one adverse event in 93% of the patients who received Trikafta® vs. 96% of the patients who received placebo. The majority of patients in the Trikafta® group had adverse events that were mild (33.2%) or moderate (50.5%) in severity. Serious adverse events occurred in 28 patients (13.9%) in the Trikafta® group vs. 42 patients (20.9%) in the placebo group. No deaths occurred during the trial. Two patients (1.0%) in the Trikafta® group (vs. no patients in

the placebo group) discontinued the trial regimen because of adverse events: rash in one patient and portal hypertension in a patient with preexisting cirrhosis. In the Trikafta® group, elevated levels of alanine aminotransferase or aspartate aminotransferase that were greater than three times, greater than five times, and greater than eight times the upper limit of the normal range occurred in 16 patients (7.9%), 5 patients (2.5%), and 3 patients (1.5%), respectively, vs. 11 patients (5.5%), 3 patients (1.5%), and 2 patients (1.0%) in the placebo group. Rash occurred in 22 patients (10.9%) in the Trikafta® group vs. 13 patients (6.5%) in the placebo group.

The most common adverse events (i.e. incidence >10%) that occurred in patients receiving Trikafta® were infective pulmonary exacerbation of cystic fibrosis (22%), increased sputum production (20%), headache (17%), cough (17%), diarrhoea (13%), upper respiratory tract infection (12%) and nasopharyngitis (11%).

In their Cochrane review, Southern et al.[19] provided statistical comparisons between Trikafta® and placebo; none of the differences were statistically significant, except for infective pulmonary exacerbation of cystic fibrosis and cough (both significantly worse in the placebo group).

Study VX19-445-116 (NCT04353817)

Mall et al. reported at least one adverse event in 80% of the children who received Trikafta® vs. 93% of the children who received placebo.[30] The majority had adverse events that were mild or moderate in severity. Serious adverse events occurred in 4 children (7%) receiving Trikafta® and in 9 children (15%) receiving placebo. No deaths occurred during the trial. One child (1.7%) in the Trikafta® group (vs. no children in the placebo group) discontinued the trial regimen because of rash. In the Trikafta® group, elevated levels of alanine aminotransferase or aspartate aminotransferase that were greater than three times, greater than five times, and greater than eight times the upper limit of the normal range occurred in 8 children (13.6%), 3 children (5.1%), and 1 child (1.7%), respectively, vs. 3 children (4.9%), 1 child (1.6%), and no children in the placebo group. Rash occurred in 8 children (13.3%) in the Trikafta® group vs. 3 children (4.9%) in the placebo group.

The most common adverse events (>10% of children) in the Trikafta® group were headache (30%), cough (23.3%), nasopharyngitis (11.7%), productive cough (11.7%) and rhinorrhoea (11.7%).

7.1.3.3 Overall incidence of adverse events

In addition to the three RCTs comparing Trikafta® with placebo, three other RCTs (comparing Trikafta® with an active control) and 22 single-arm studies provided primary information on the safety of Trikafta®.[36-57] Furthermore, 4 systematic reviews[17-20] and 7 HTA reports[4, 5, 21-25] reported on the safety of Trikafta®. From all these studies a frequency table was constructed informing about the overall incidence of adverse events related to the use of Trikafta® (Table 11).

Many of the more frequent adverse events can be related to cystic fibrosis, such as cough, pulmonary exacerbation, increased sputum production, etc. Some frequent adverse events, however, warrant attention. Increased use of psychiatric medication[57] and an increased incidence of

psychiatric disorders[43] was reported by two studies. Headache was reported in a rather high frequency in 12 studies and gastrointestinal symptoms in 11 studies. Serious adverse events included rash, hepatic adverse events (liver function tests) and distal intestinal obstruction syndrome.

Table 11: Overview of reported adverse events of Trikafta® in published literature

Adverse event	N reported cases	Total population	Percentage	N studies
Adverse events, general[29-32, 34, 35, 40-43, 49, 55, 56]	1272	1608	79.1%	13
Very frequent: incidence of at least 10%				
Cough[29-31, 35, 41, 55, 56]	252	1059	23.8%	7
Increased psychiatric medication[57]	22	100	22.0%	1
Infective pulmonary exacerbation[29-31, 35, 41, 43]	199	957	20.8%	6
Rhinorrhoea[30, 55]	23	124	18.5%	2
Nasal congestion[55, 56]	24	130	18.5%	2
Pyrexia[29, 55, 56]	37	204	18.1%	3
Gastrointestinal symptoms: constipation[55]	10	64	15.6%	1
Increased sputum production[29, 31, 35, 41]	133	869	15.3%	4
Gastrointestinal symptoms: vomiting[55, 56]	19	130	14.6%	2
Hepatic adverse events: Liver function tests: TA, 2x ULN[43]	4	28	14.3%	1
Neurological symptoms[43]	4	28	14.3%	1
Psychiatric disorders[43]	4	28	14.3%	1
Headache[30-32, 34, 35, 37, 41-44, 55, 56]	236	1708	13.8%	12
Oropharyngeal pain[30, 31, 35, 41, 55, 56]	132	985	13.4%	6
Nasopharyngitis[30, 31, 35, 41, 55]	123	919	13.4%	5
Productive cough[30, 55]	15	124	12.1%	2
Upper respiratory tract infection[31, 35, 41, 55, 56]	108	925	11.7%	5
Gastrointestinal symptoms: general[37, 43, 44]	37	338	10.9%	3
Recurrent bacterial infections[43]	3	28	10.7%	1
Wheezing[43]	3	28	10.7%	1
Dizziness[42]	2	20	10.0%	1
Dry eyes[42]	2	20	10.0%	1

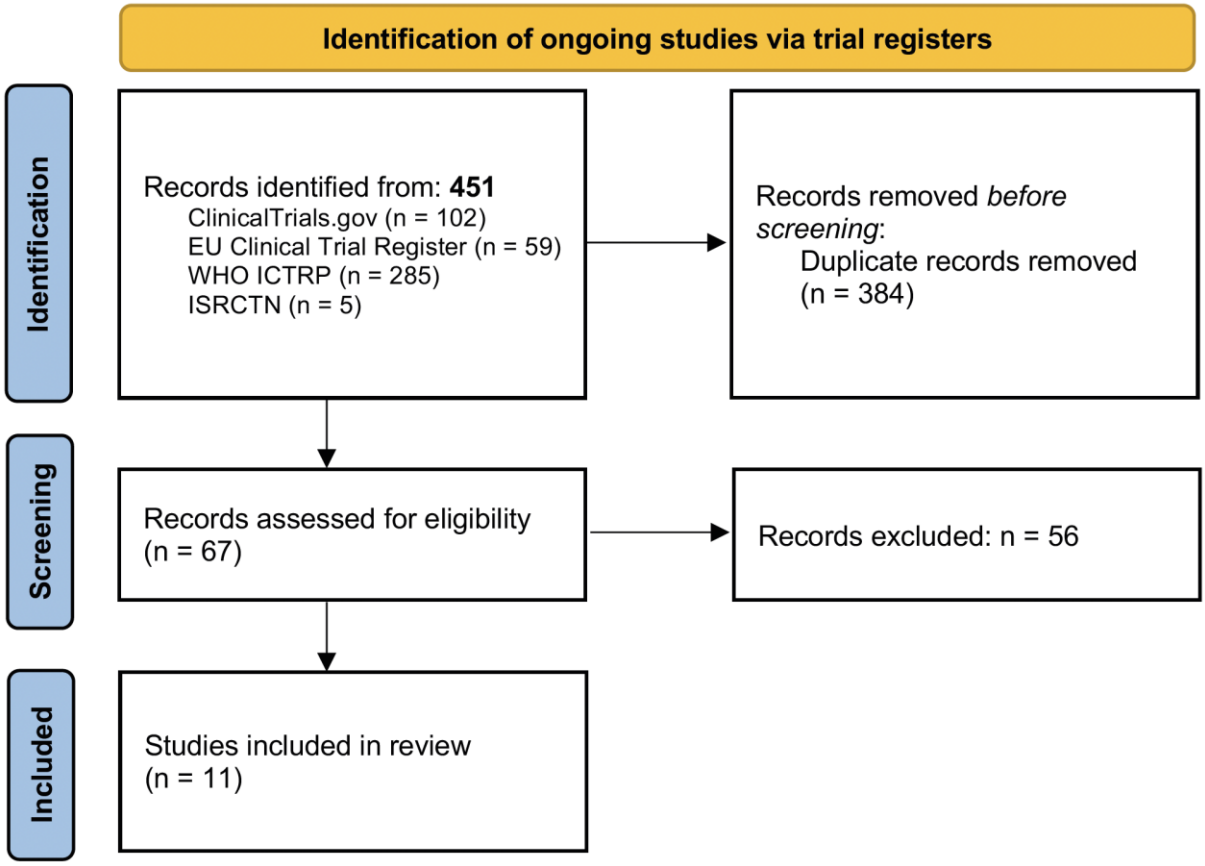
Adverse event	N reported cases	Total population	Percentage	N studies
Gastrointestinal symptoms: discolored stool[42]	2	20	10.0%	1
Frequent: incidence between 1% and 10%				
Rash[30-32, 34, 35, 40-43, 47, 49, 51, 55, 56]	138	1594	8.7%	14
Gastrointestinal symptoms: diarrhoea[31, 32, 42, 49, 55, 56]	54	632	8.5%	6
Fatigue[31, 41]	60	708	8.5%	2
Hepatic adverse events: general[40]	9	114	7.9%	1
Gastrointestinal symptoms: abdominal pain[30, 32, 40, 42, 49, 55, 56]	47	604	7.8%	7
Rash, localised cutaneous[37, 44]	24	310	7.7%	2
Hepatic adverse events: Liver function tests: TA, 3x ULN[29-32, 34, 35, 41, 42, 44, 55]	109	1443	7.6%	10
Hepatic adverse events: Liver function tests: CK, 2x ULN[43]	2	28	7.1%	1
Testicular tenderness[43]	2	28	7.1%	1
Hepatic adverse events: Liver function tests: ALT, 3x ULN[36, 37, 52]	949	16616	5.7%	3
Myalgia[37, 44]	17	310	5.5%	2
Gastrointestinal symptoms: flatulence[42]	1	20	5.0%	1
Hair loss[42]	1	20	5.0%	1
Hypercholesterolemia[42]	1	20	5.0%	1
New mental health diagnosis[57]	5	100	5.0%	1
Hepatic adverse events: Liver function tests: bilirubin, 3x ULN[37]	12	245	4.9%	1
Treatment interruption[29, 35, 37, 39, 41, 46, 50-52, 55, 56]	54	1381	3.9%	11
Hepatic adverse events: Liver function tests: bilirubin, 2x ULN[29, 36, 54]	632	16270	3.9%	3
Rash, generalized cutaneous[37, 44]	12	310	3.9%	2
Distal intestinal obstruction syndrome[29, 46]	3	88	3.4%	2
Hepatic adverse events: Liver function tests: CK, 3x ULN[37, 47]	9	291	3.1%	2

Adverse event	N reported cases	Total population	Percentage	N studies
Hepatic adverse events: Liver function tests: AST, 3x ULN[36, 37, 52]	508	16616	3.1%	3
Hepatic adverse events: Liver function tests: TA, 5x ULN[30-32, 34, 35, 41, 55]	37	1284	2.9%	7
Hepatic adverse events: Liver function tests: CK, 5x ULN[37, 44, 56]	7	376	1.9%	3
Hepatic adverse events: Liver function tests: ALT, 5x ULN[36, 37, 52, 54]	299	16696	1.8%	4
Treatment discontinuation[29-32, 34, 35, 37, 40-42, 44, 45, 49, 50, 55, 56]	30	1917	1.6%	16
Gastrointestinal symptoms: nausea[32]	4	258	1.6%	1
Hepatic adverse events: Liver function tests: AST, 5x ULN[36, 52]	193	16371	1.2%	2
Treatment interruption because of elevated TA[29, 34, 47, 55, 56]	4	357	1.1%	5
Less frequent: incidence <1%				
Treatment discontinuation because of elevated TA[30, 32, 34, 35, 40, 41, 43, 48, 55, 56]	12	1384	0.9%	10
Hepatic adverse events: Liver function tests: TA, 8x ULN[30-32, 34, 41, 55]	9	1197	0.8%	6
Hepatic adverse events: Liver function tests: ALT, 8x ULN[36, 52, 54, 56]	99	16517	0.6%	4
Hepatic adverse events: Liver function tests: AST, 8x ULN[36, 52, 56]	81	16437	0.5%	3
Hepatic adverse events: Liver function tests: CK, 11x ULN[37]	1	245	0.4%	1
Arterial hypertension[30, 32, 53, 56]	1	440	0.2%	4
Deaths[29-32, 34, 39, 41, 45, 50, 55, 56]	0	1411	0.0%	11

7.1.4 Ongoing trials

The search in the clinical trial registers yielded a total of 451 hits. After de-duplication (384 hits), 67 unique records were screened for eligibility. Of these, 56 references were excluded, while 11 ongoing trials were included (Figure 6).

Figure 6: PRISMA flow chart for the identification of ongoing trials



One ongoing RCT was identified to be relevant for the safety information (NCT05274269). In this study 307 patients aged 6 years and older with cystic fibrosis and a non-F508del elexacaftor-tezacaftor-ivacaftor (ELX/TEZ/IVA)-responsive CFTR mutation were randomized to Trikafta®, Ivacaftor or a matching placebo. The study is reported to be completed, but no results were published yet.

The 10 other ongoing studies are single cohort studies that will provide additional information about the safety of Trikafta®.

Table 12: Overview of ongoing studies about Trikafta®

Study ID	Study type	Status	Enrollment
NCT05274269 **VX21-445-124** **EudraCT 2021-005320-38**	RCT	Completed Not published	307
EudraCT 2020-005224-12 **KAFTAC2020**	Single cohort study	Ongoing End date: unclear	5
ACTRN12623000595617	Single cohort study	Ongoing End date: December 2024	Target: 210
NCT04043806 **VX18-445-113** **EudraCT 2018-004652-38**	Single cohort study	Completed Not published	458
NCT04058366 **VX18-445-110** **EudraCT 2019-000833-37**	Single cohort study	Completed Not published	251
NCT04362761 **VX19-445-115** **EudraCT 2019-003455-11**	Single cohort study	Completed Not published	172
NCT04545515 **VX20-445-119**	Single cohort study	Completed Not published	120
NCT04599465 **VX19-445-117**	Single cohort study	Completed Not published	69
NCT05111145 **VX20-445-121** **EudraCT 2020-004885-21**	Single cohort study	Completed Not published	86
NCT05153317 **VX20-445-112**	Single cohort study	Ongoing End date: April 2026	70
NCT05331183 **VX21-445-125**	Single cohort study	Ongoing End date: April 2025	297

7.1.5 Summary of key findings

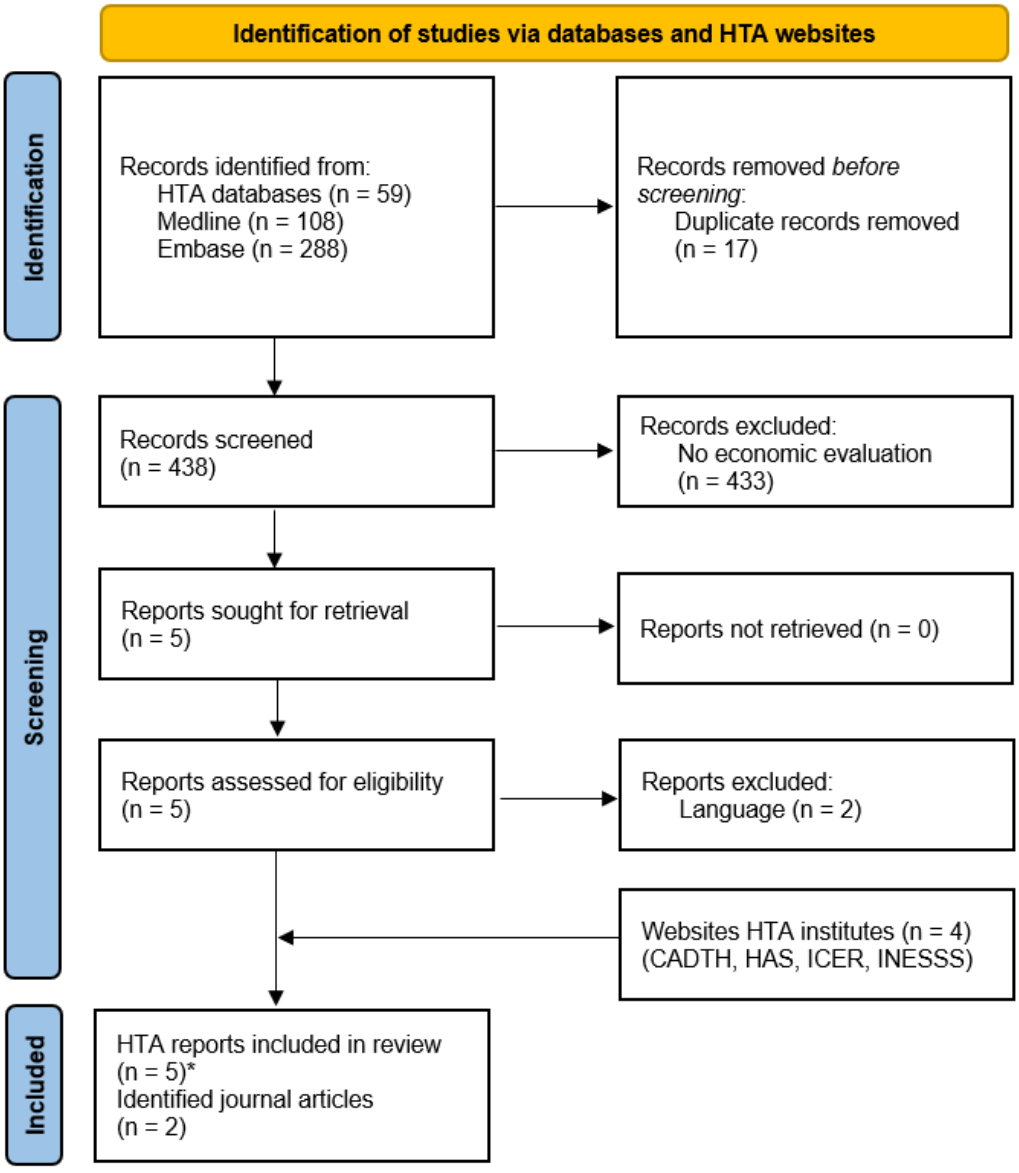
- Three RCTs compared Trikafta® with standard of care (placebo) in patients aged 6 and older with cystic fibrosis who have one F508del mutation and one minimal function mutation in the CFTR gene (F/MF).
- No RCTs were published that compared Trikafta® with standard of care (placebo) in patients aged 6 and older with cystic fibrosis who are homozygous for F508del mutation (F/F), who have one F508del mutation and one residual function mutation in the CFTR gene (F/RF), or who have one F508del mutation and one gating mutation in the CFTR gene (F/G).
- For patients aged 6 and older with cystic fibrosis who are homozygous for F508del mutation (F/F), a network meta-analysis is available comparing Trikafta® with standard of care (placebo).
- The available RCTs and network meta-analysis provide consistent high-quality evidence for the effectiveness of Trikafta® in comparison with standard of care up to 24 weeks. Beyond 24 weeks, an open-label extension of two RCTs provides non-randomized follow-up data up to 48 weeks, and appears to confirm the effectiveness of Trikafta®. Follow-up data beyond 48 weeks are only available from (extensions of) single-arm studies.
- From the available RCTs no data on mortality are available, nor are data on quality of life measured with a generic utility instrument.
- Trikafta® has been shown to be a safe intervention (with follow-up up to 96 weeks), with most of the reported adverse events being related with the underlying disease (i.e. cystic fibrosis). Adverse events that warrant attention are psychiatric disorders, headache and gastrointestinal symptoms because of frequency, and rash, hepatic adverse events and distal intestinal obstruction syndrome because of severity.

7.2 Review of economic evaluations

7.2.1 Search results

The search for economic evaluations on INAHTA's HTA database, Medline and Embase identified 455 references. After de-duplication, 438 remaining references were screened based on title and abstract, of which 433 were excluded because of the study type (no economic evaluation, see Figure 7). Based on the full-text evaluation, one HTA report and two journal articles were selected. Searching the websites of INAHTA members identified another four HTA reports.

Figure 7: PRISMA flow chart for the identification of economic evaluations



* For both CADTH and ZIN, two reports are presented in Table 13. We count these as one, resulting in a total of 5 HTA reports.

CADTH: Canadian Agency for Drugs & Technologies in Health; HAS: Haute Autorité de Santé; HTA: Health Technology Assessment; ICER: Institute for Clinical and Economic Review; INESSS: Institut National d'Excellence en Santé et en Services Sociaux.

Table 13 shows an overview of the identified economic evaluations. The publications that refer to the same economic evaluation are clustered. For example, the journal article of Tice et al.[59] refers to the ICER report. This HTA report of the ICER institute is included in our overview since the authors also performed a scenario analysis in which they assumed a start age of 6 years instead of 12 years for Trikafta® treatment. We remark that CADTH and Haute Autorité de Santé (HAS) also published a separate HTA report for assessing the use of Trikafta® in patients older than 12 years.[21, 60] These reports were not included in the overview since they also published an assessment specifically for patients older than six years, which is already included in our overview.

In the ZIN assessment,[25] it is mentioned that a financial arrangement was already negotiated for Trikafta®. Therefore, ZIN decided not to perform a cost-effectiveness analysis for the assessment of extending the conditions for using the combination therapy in cystic fibrosis. As a result, this report is not included in our overview. Nevertheless, the report will be used to provide input for the variables used in the context-specific evaluation.

Finally, the journal article of Rubin et al.[61] explores alternative assumptions for discounting, utility measures, disease management costs, and static drug pricing. Several of these alternative assumptions are discussed in the selected HTA reports. Therefore, we do not separately include this paper in our overview but prefer to reflect the assessment of the HTA institutes about these alternative assumptions which impact cost-effectiveness outcomes.

In the end, the CADTH,[4] HAS,[62] ICER[5] and Institut National d'Excellence en Santé et en Services Sociaux (INESSS)[63] HTA reports are included in our literature overview.

Table 13: Overview of identified economic evaluations

HTA organization	Reference
CADTH	– (1a) CADTH. Elexacaftor-Tezacaftor-Ivacaftor and Ivacaftor (Trikafta®). CADTH reimbursement review. Canadian Agency for Drugs and Technologies in Health (CADTH). Canadian Journal of Health Technologies. September 2022, Volume 2, Issue 9. 383 pages.[4] – (1b) CADTH. Elexacaftor-Tezacaftor-Ivacaftor and Ivacaftor (Trikafta®). CADTH reimbursement recommendation. Canadian Agency for Drugs and Technologies in Health (CADTH). Canadian Journal of Health Technologies. July 2022, Volume 2, Issue 7. 32 pages.[64]
HAS	(2) HAS. Kaftrio® (elexacaftor/tezacaftor/ivacaftor) en association à l'ivacaftor. Mucoviscidose chez les patients âgés de 6 ans et plus avec au moins une mutation F508del du gène CFTR. Avis économique. Haute Autorité de Santé (HAS). Octobre 2022. 89 pages.[62]
ICER	(3) ICER. Modulator treatments for cystic fibrosis: effectiveness and value. Institute for Clinical and Economic Review (ICER). September 2020. 340 pages.[5] – Remark: Initially, this report was excluded since in the base case, patients assigned to lifetime Trikafta® therapy switch to this therapy at age 12. However, this report was included since the authors also performed a scenario analysis in which they assumed a start age of 6 years instead of 12 years, anticipating that younger patients would be eligible for this drug in the near future. – The following journal article is based on the above HTA report: Tice JA, Kuntz KM, Wherry K, Seidner M, Rind DM, Pearson SD. The effectiveness and value of novel treatments for cystic fibrosis. J Manag Care Spec Pharm. 2021;27(2):276-80.[59]
INESSS	(4) INESSS. Trikafta® – traitement de la fibrose kystique. Institut National d'Excellence en Santé et en Services Sociaux (INESSS). Juillet 2022. 30 pages.[63]
ZIN	(5) ZIN. GVS-advies elexacaftor/tezacaftor/ivacaftor (Kaftrio®) in combinatie met ivacaftor (Kalydeco®) – uitbreiding nadere voorwaarden. Zorginstituut Nederland (ZIN). Maart 2022. 87 pages.[25]

	– Remark: In the Netherlands, a financial arrangement was already negotiated for all current and future indications of elexacaftor/tezacaftor/ivacaftor. Therefore, in this ZIN assessment, it was decided not to perform a cost-effectiveness analysis for the assessment of extending the conditions for using the combination therapy in cystic fibrosis. Nevertheless, to gather further information on the input variables used in the economic evaluation, the original evaluation for patients older than 12 years is used to provide input for the context-specific economic evaluation. The reference of this report is the following: ZIN. GVS-advies elexacaftor/tezacaftor/ivacaftor (Kaftrio®) in combinatie met ivacaftor (Kalydeco®). Zorginstituut Nederland (ZIN). April 2021. 173 pages.[24]
Others	Rubin JL, Lopez A, Booth J, Gunther P, Jena AB. Limitations of standard cost-effectiveness methods for health technology assessment of treatments for rare, chronic diseases: a case study of treatment for cystic fibrosis. Journal of Medical Economics. 2022;25(1):783-791.[61] – In this analysis, the authors explore how alternative assumptions for (1) discounting, (2) utility measures, (3) disease management costs, and (4) static drug pricing impact cost-effectiveness outcomes. These alternative assumptions are discussed in several of the above HTA reports and included in the discussion of this report.

CADTH: Canadian Agency for Drugs and Technologies in Health; HAS: Haute Autorité de Santé; ICER: Institute for Clinical and Economic Review; INESSS: Institut national d'excellence en santé et en services sociaux; ZIN: Zorginstituut Nederland

7.2.2 Study characteristics

As mentioned in the methods section, at this stage, we provide the information as provided in the identified economic evaluations, as well as the assessment of the authors of these HTA reports.

7.2.2.1 General characteristics

The identified economic evaluations are performed for Canada (2), France (1) and the US (1) (Table 14). There is a partial conflict of interest since the sponsor (Vertex Pharmaceuticals) submitted the economic evaluation of Trikafta®/Kaftrio® presenting their own calculations. An appraisal was performed by the independent HTA institutes, identifying key limitations and adjusting the economic evaluation. These institutes are free of CoI.

All studies performed a cost-utility analysis (cost per QALY). In most analysis, life-years (gained) are also calculated, but incremental cost-effectiveness ratios are only presented per QALY gained. All reports refer to a patient-level microsimulation model. More information is provided in part 7.2.2.3.

The analyses are performed from different perspectives. CADTH refers to a publicly funded health care payer. HAS explicitly refers to both the compulsory health insurance and any other payer (i.e. also the patient). The ICER report first considered a dual base-case analyses that reflect both health care system and societal perspectives if the impact of the treatment on patient and caregiver productivity, education, disability and nursing home costs were large relative to health care costs. However, because they did not find this to be the case, they present the societal perspective only as a scenario analysis.[5] Finally, the INESSS analysis is carried out from a societal perspective.

Both CADTH and ICER apply a lifetime horizon. HAS applies a time horizon and includes the lifetime horizon in their scenario analyses. Costs and effects are equally discounted, at 1.5%,[4] 2.5%,[62] and 3%[5] per year in the base-case analysis. In the HAS analysis, the discount rate is gradually reduced to 1.5% after 30 years.[62] In the INESSS report,[63] neither the time horizon nor the discount rates for costs and effects are reported.

Table 14: General characteristics of the identified economic evaluations

	Country	CoI	Analytic technique	Type of model	Perspective	Time horizon	Discount rate
CADTH (2022)	Canada	Y/N	CUA*	Microsimulation	Public health care payer (government)	Lifetime (appr. 92 years)	C&E: 1.5%
HAS (2022)	France	Y/N	CUA	Microsimulation	Health care payer (government and patient)	40 years	C&E: 2.5% for 30 years; gradual decrease to 1.5%
ICER (2020)	US	Y/N	CUA**	Microsimulation	Health care system (societal)	Lifetime	C&E: 3%
INESSS (2022)	Canada	Y/N	CUA	Microsimulation	Societal	NR	NR

Appr.: approximately; C: cost; CoI: conflict of interest; CUA: cost-utility analysis; E: effect; N: no; NR: not reported; Y: yes.

* CUA: in all identified reports, results are expressed in extra cost per quality-adjusted life-year (QALY) gained. In most analyses, life-years are also calculated, but results are not expressed in extra cost per life-year gained (LYG). ** In the ICER report, equal value life years gained (evLYGs) and lifetime number of acute pulmonary exacerbations were also used as an outcome. However, in our overview, we focus on the outcomes expressed in QALYs gained.

7.2.2.2 Population, intervention and comparator

The population includes patients with CF aged 6 to 11 years or 6 years and older who have at least one F508del mutation in the CFTR gene (Table 15). In the ICER report, the base case analysis includes patients switching to lifetime Trikafta® therapy at age 12. However, anticipating that the eligibility age for this therapy would be lowered, an extra analysis was conducted starting Trikafta® therapy at 6 years.[5]

The following 4 genotypes were considered in the HTA reports: homozygous for F508del-CFTR (F/F); heterozygous for F508del-CFTR with a minimal function mutation (F/MF); heterozygous for F508del-CFTR with a residual mutation (F/RF); and heterozygous for F508del with a gating

mutation (F/G). In the CADTH analysis, all 4 genotypes were considered in separate analyses. In the HAS analysis this was limited to the F/F and F/MF genotypes. The ICER report performed scenario analysis for three genotypes (F/F, F/MF and F/RF). Finally, in the INESSS report, the company submitted analyses per genotype. The results of these 4 analyses are kept confidential and cannot be included in our overview. Although the authors of the INESSS report state confidence in clinical inputs vary according to genotype, they do not consider it appropriate for their evaluation to separate the results into different types of analysis.[63] Therefore, in the INESSS report, the results of the analysis are homogenized within a single ICER.

The intervention is Trikafta®/Kaftrio®, given at the recommended dosage of two tablets of ELX-TEZ-IVA taken in the morning and one tablet of IVA taken in the evening. The treatment is given in combination with best supportive care (BSC). In the comparator group, BSC is given in all analyzed genotypes. In the CADTH analysis, BSC consists of recommended medications (such as mucolytics, inhaled and oral antibiotics, inhaled hypertonic saline, nutritional supplements, enteral tube feeding, pancreatic enzymes, antifungal agents, and corticosteroids) and physiotherapy.[4]

Next to BSC, the CADTH analysis also includes a comparison with LUM-IVA in the F/F subgroup and IVA monotherapy in the subgroup of patients with a F/G genotype.[4] In the HAS analysis, LUM-IVA and TEZ-IVA are included as a comparator in the F/F subgroup.[62] The ICER report only compared with best supportive care alone and did not compare CFTR modulator treatments directly with each other.[5] A similar approach is followed in the INESSS report.

Table 15: Population, intervention and comparator in the identified economic evaluations

	Population	Intervention	Comparator
CADTH (2022)	Patients aged 6 to 11 years Patients ≥6 years of age • F/F genotype • F/MF genotype • F/RF genotype • F/G genotype	Trikafta® + BSC*	BSC (all genotypes) F/F: LUM-IVA** F/G: IVA**
HAS (2022)	Patients ≥6 years of age • F/F genotype • F/MF genotype	Kaftrio® + BSC	BSC (F/F and F/MF) F/F: LUM-IVA; TEZ-IVA**
ICER (2020)	Patients ≥12 years of age Scenario: ≥6 years • F/F genotype • F/MF genotype • F/RF genotype	Trikafta® + BSC	BSC
INESSS (2022)	Patients aged 6 to 11 years Patients ≥6 years of age • F/F; F/MF; F/RF; and F/G genotype	Trikafta® + BSC	BSC

BSC: best supportive care; IVA: ivacaftor; LUM-IVA: lumacaftor-ivacaftor (Orkambi®); TEZ-IVA: tezacaftor/ivacaftor (Symkevi®). F/F: homozygous for F508del-CFTR; F/G: heterozygous for F508del with a gating mutation; F/MF: heterozygous for F508del-CFTR with a minimal function mutation; F/RF: heterozygous for F508del-CFTR with a residual mutation.

* The product name Trikafta®/Kaftrio® is used as applied in the underlying reports. When mentioning these therapies, it is assumed that best supportive care is also given. Therefore, the term BSC will no longer be explicitly added when referring to Trikafta®/Kaftrio® treatment.

** Other CFTR modulators are originally included as an active comparator. However, in the original research question, BSC is the relevant comparator. We come back to this in the discussion.

7.2.2.3 Type of model – microsimulation

In all economic evaluations, a patient-level microsimulation model is used. Initially, each simulated patient is assigned a ppFEV1 value drawn from a distribution and then experiences annual age-specific declines in lung function.[5] At the beginning of each cycle, the model calculates a patient's mortality risk. Differences are noticed in the general description of variables included in this formula. According to the description provided in the HTA reports, the following characteristics were included in the calculation of mortality risk:

– CADTH: age, sex, ppFEV1, annual number of pulmonary exacerbations, prior respiratory infection status, CF-related diabetes, weight-for-age z scores, and pancreatic sufficiency status.[4]
– HAS: age, ppFEV1, pulmonary exacerbations, CF-related diabetes, weight-for-age z scores, lung transplantation, the occurrence of adverse events, and treatment discontinuation.[62]
– ICER: age, sex, ppFEV1, CF-related diabetes, weight-for-age z scores, pancreatic sufficiency status, and age at B.cepacia infection.[5]
– INESSS: FEV1, weight-for-age Z-score, pulmonary exacerbation rate, eligibility for lung transplantation and the presence or absence of diabetes.[63]

Only the ICER report[5] transparently provides the underlying equation used to model the annual mortality rate for non-transplanted patients:[65]

$$h_a = b_a e^{(K)}$$

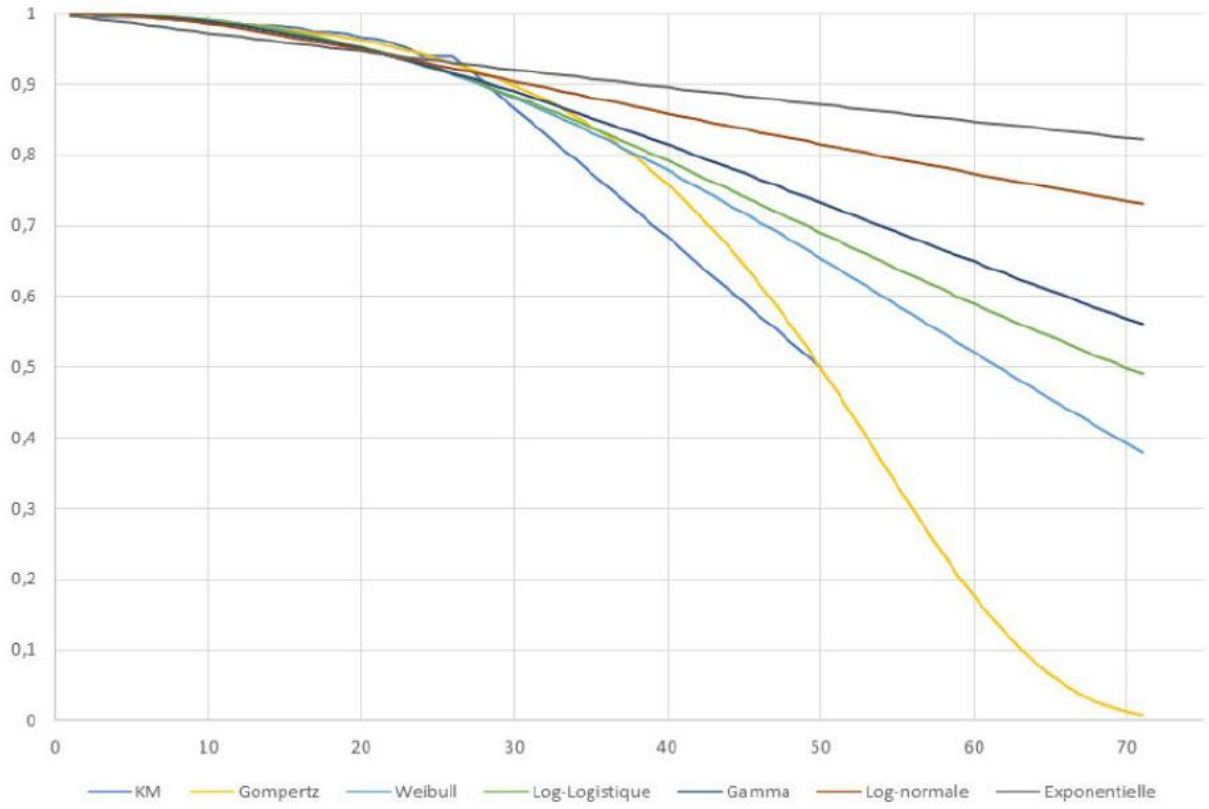
$$K = 0.15(SEX - 0.47) - 0.042(ppFEV_1 - 67.7) - 0.0280(WFA + 0.85) + 0.350(\#PE - 1.1) + 0.440(DIAB - 0.061) - 0.140(PS - 0.053) + 1.410(BAI - 0.032) - 0.280(\#PE - 1.1)(BAI - 0.032)$$

Source: ICER report.[5] It is stated that "the patient-specific parameters that affect mortality among non-transplanted patients were SEX (0 male, 1 female), ppFEV1 (%), WFA (weight-for-age z score), #PE (number of acute pulmonary exacerbations in the current year), DIAB (0 no diagnosis of diabetes, 1 yes), PS (0 no pancreatic sufficiency, 1 yes), BAI (0 no B. cepacia infection, 1 yes). The age-specific baseline hazard (ba) was a product of the age-specific rates from the US life tables[66] and an adjustment factor that was needed to match the life expectancy targets of a CF cohort." The adjustment factor is not reported.

In the description of the above equation, it is mentioned that an adjustment factor is applied to match the life expectancy targets of a CF cohort. These details are unfortunately not provided in the ICER report.

The approach to fit a survival function is described in the HAS (2021) report.[60] First, the manufacturer chose a median survival rate of 50 years for CF patients without CFTR modulator treatment. This median survival was based on a study of registry data which estimated the survival rate of French patients with CF using two methods, resulting in a median survival of 49.3 or 57.6 years depending on the method. It was mentioned that the review by Scotet et al.[67] also supported this hypothesis, with a median survival estimated between 44 and 52 years in the United States, England, Ireland and Canada in 2018. Second, the Kaplan-Meier (KM) curve completed by the median survival rate of 50 years was extrapolated via the application of a parametric function, selected according to the Akaike information criterion (AIC) and Bayesian information criterion (BIC) as well as the clinical plausibility of the curves obtained. The Gompertz function was selected for the reference analysis, simulating an extinction of the cohort around age 70. The curve obtained is presented in Figure 8. HAS judged this approach to be acceptable.

Figure 8: Graphical representation of the different survival functions adjusted to the data observed in the French cystic fibrosis registry, applying a median survival of 50 years

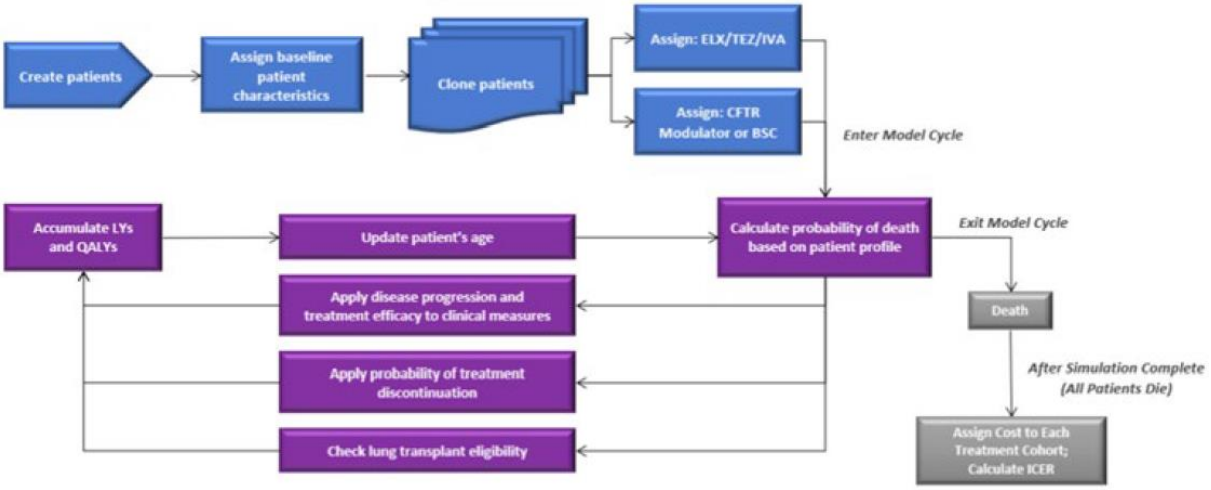


* Source: Figure 5 from the HAS (2021) report.[60] X-axis: age; y-axis: proportion of patients alive.

To model the survival function for the intervention group, Trikafta® treatment is assumed to affect disease progression and mortality through effects relating to ppFEV1, weight-for-age z scores, and pulmonary exacerbation rates.[4] More details on the modelled treatment effect are available in part 7.2.2.5. Every cycle, patients might also undergo a lung transplantation if their ppFEV1 falls under a specific level (also see part 7.2.2.5).

The following figure from the CADTH report reflects the model structure. Similar figures are presented in the HAS and ICER reports.

Figure 9: Model structure applied in the identified economic evaluations



* Source: Figure 1 from the CADTH report referring to the Sponsor's pharmacoeconomic submission.[4]

7.2.2.4 Model input – costs

Table 16 provides an overview of the costs used in the identified economic evaluations. In general, no detailed information could be extracted from the INESSS report which lacks transparency. The CADTH report provides a description of included costs, but does not always provide full details for the applied costs for all listed items. The HAS and ICER reports provide the most details. However, HAS remarks that no analysis of treatment costs has yet been carried out in the French context and wants the manufacturer to conduct analyses on French databases.[62]

The recommended dosage of ELX-TEZ-IVA for patients aged 6 to less than 12 years who weigh less than 30kg is a combination of two tablets in the morning (each containing ELX 50mg, TEZ 25mg, and IVA 37.5mg) and one standalone tablet (containing IVA 75mg) taken in the evening. For those aged 6 to less than 12 years who weigh 30kg or more and those 12 years and older, the recommended dosage is two combination tablets in the morning (each containing ELX 100mg, TEZ 50mg, and IVA 75mg) and one standalone tablet (containing IVA 150mg) taken in the evening.[4] Lower doses (for younger patients) have the same price as adult doses, so no age adjustments were made.[5] The CFTR modulators are administered orally. Therefore, no additional administration costs are considered.[4, 5, 62] The annual Trikafta® treatment cost per patient is as follows: CAD306 810;[4] €207 522;[62] $311 741;[5] and CAD305 760[63] .[b] For the yearly treatment cost of other CFTR modulators, we refer to Table 16.

In the CADTH report, the manufacturer employed a dynamic pricing approach, whereby the introduction of a first generic into the market after the loss of patent exclusivity would lead to a 25% reduction in the prices of all drugs (after 18 years for Trikafta®[c]), followed by a second generic

[b] In the economic literature review, cost information is presented in the original currency. The exchange rate on 7 January 2024 for the relevant currencies in this report are as follows: CHF1 = €1.0743 = $1.1768 = CAD1.5717.
[c] No further details are provided related to the date of loss of patent exclusivity. Companies typically apply for patents several years before a product receives marketing approval, which 'under current law" expires 20 years from its first effective filing date.

entry further reducing their prices by 50% (after 19 years for Trikafta®).[4] The CADTH reviewers did not follow this approach. Similarly, in the ICER report, it was explicitly stated not to include such an assumption, because attempts to model price changes over time would add an additional layer of uncertainty and speculation to the analysis.[5] The ICER assessors[5] stated that "the current convention is not to include estimates of changes in drug price throughout the life cycle.[68, 69] The assumption of a large price drop at patent expiry was considered to be a limitation and not appropriate in CADTH's Common Drug Reviews of the economic models submitted for Kalydeco® and Orkambi®, and was not recommended as a base case assumption for the UK NICE appraisal committee's assessment of Orkambi®.[70-74] "

Furthermore, in the manufacturer's submission, the costs associated with Trikafta® were adjusted for compliance. Non-adherence to treatment is included in the model in the form of a coefficient associated with acquisition costs. In the CADTH report, a compliance of 93% is assumed by the manufacturer.[4] In the HAS report, during the RCT period, the manufacturer applied the compliance rate based on clinical trial results. In the post-RCT period, compliance rates were based on a retrospective US database study evaluating the impact of ivacaftor (Kalydeco®) on healthcare resource utilisation based on US administrative claims data.[75] This study showed that among 79 CF patients aged 6 years and older who were prescribed ivacaftor, the mean drug compliance rate was 80%. An identical rate of 80% was therefore applied in the manufacturer's calculation for CFTR modulator treatments beyond the clinical trial period and until the end of the time horizon.[62] According to HAS, this rate is not sufficiently discussed, especially as the extrapolation of efficacy data is based on a compliance rate close to 100% (observed during the clinical trial) and the reduction in compliance applied after the clinical trial is likely to reduce the efficacy observed. The compliance rate incorporated into the model therefore takes into account increased efficacy and reduced treatment costs, which has a significant impact on the results. For HAS, this is an important limitation.[62]

In the CADTH and HAS report, it is mentioned that additional costs associated with CFTR-modulator use include monitoring costs consisting of liver function tests and ophthalmologist visits. An ophthalmological consultation is included at the start of the simulation for all patients initiating treatment with CFTR modulators.[62] Monitoring of liver function occurs before initiating treatment, every 3 months during the first year, and then at least once a year in the following years.[62] In contrast, in the ICER report, it is assumed that there were no additional costs associated with the administration and monitoring of the CFTR drugs above best supportive care.

Next to costs related to Trikafta®, there are three large groups of CF-related health care costs included in the models: disease management, acute pulmonary exacerbations requiring IV antibiotics, and lung transplant-related costs. In all models, disease management and pulmonary exacerbation costs are linked to ppFEV1 to reflect increasing costs with increasing disease severity:[4, 5,

The expiration of the US and EU patent protection is projected in 2037 (Source: https://www.sec.gov/Archives/edgar/data/875320/000087532020000007/a201910k-main.htm).

[62] ppFEV1 ≥70% (mild disease); ppFEV1 ≥40-69% (moderate disease); and ppFEV1 <40% (severe disease). As such, slowing down the decline in lung function results in additional cost savings.

– Disease management costs:

  In the CADTH analysis, in addition to the costs based on ppFEV1 level, costs are specific for children (<18 years) or adult population. The manufacturer further adjusted the disease-management costs specific to inpatient visits and pharmacotherapy for patients on CFTR modulators, based on studies in the literature that indicated a reduction in CF-related inpatient admissions and outpatient IV and antibiotic use.[76, 77] As a result, differential annual inpatient costs and annual pharmacotherapy costs were estimated for patients on BSC alone and those on CFTR modulators.[4] The CADTH assessors did not agree with this further distinction and only included differential costs related to the ppFEV1 level (see Table 16). Also the HAS and ICER assessors assumed that best supportive care applied to all individuals, whether on CFTR modulators or not, and that the intensity of therapy only varied by lung function category.[5, 62] In the ICER report,[5] it was allowed that the intensity of best supportive care was reduced by Trikafta®, independent of lung function, in a scenario analysis.

  In the CADTH report, the manufacturer excluded disease-management costs in the intervention arm for patients on CFTR modulators after a similar patient on BSC in the comparator arm had died in a given simulation, while only incurring costs for CFTR-modulator therapy for the remainder of the time horizon in the intervention arm.[4] This is not considered appropriate by the assessors.

  Finally, in the ICER report, the assessors explicitly state disease management costs will vary as individuals who live longer will have higher management costs, although individuals on modulator therapy will also have better lung function, resulting in reductions in these costs.[5]

– Acute pulmonary exacerbations requiring IV antibiotics:

  In the CADTH analysis, it is also mentioned that costs are further divided into costs related to pulmonary exacerbations and non-pulmonary exacerbations. Unfortunately, no further details are provided. In the HAS and ICER analyses, it is mentioned that only exacerbations leading to IV antibiotic therapy or hospitalization are taken into account. In the HAS analysis,[62] the annual pulmonary exacerbations costs are part of the annual pathology follow-up costs per ppFEV1 category. For transparency, these costs are also presented separately. In contrast, in the ICER report, it is assumed that acute pulmonary exacerbations treated with oral therapy in an ambulatory setting are included in the disease management costs. However, acute pulmonary exacerbations requiring IV antibiotics were costed separately and also varied by level of ppFEV1.[5] Both the HAS and ICER analyses included an age-related adjustment (< or ≥18 years).

– Lung transplant:

  In the CADTH report, it is mentioned that lung transplantation costs were obtained from Alberta Health Services, with follow-up costs obtained from the literature.[78, 79] However, no further cost

details were provided. In the HAS report, post-transplantation costs include costs for treatments and hospitalizations, outpatient consultations, and additional examinations. These annual costs decrease over the years (see Table 16). We could not find cost information related to the initial lung transplantation. In the ICER report, transplant-related costs include the one-time cost of receiving a lung transplant followed by an annual cost associated with post-transplantation care. In this post-transplant period, the CF-related disease management costs were assumed to be 41% of the costs prior to transplant (i.e., costs associated with the lowest lung function category) to represent non-pulmonary CF-related costs,[80] and exacerbation costs were assumed to be zero (i.e., exacerbations do not occur).[5]

Table 16: Costs included in the identified economic evaluations

	CADTH (2022)	HAS (2022)	ICER (2020)	INESSS (2022)
Currency, year	Canadian dollar (CAD), NR	Euro (€), 2021	US dollars ($), 2019	Canadian dollar (CAD), NR
Trikafta®	CAD306 810/year	€207 522/year	$311 741/year	CAD305 760/year
Other CFTR modulators	IVA: CAD306 810/year LUM-IVA: CAD249 153/year	LUM-IVA (Orkambi®): €132 850/year TEZ-IVA (Symkevi®): €134 139/year	NA	NA
Dynamic pricing	Manufacturer applied dynamic pricing for Trikafta®: • 25% price reduction after 18 years • 50% price reduction after 19 years CADTH: no dynamic pricing	NR (no dynamic pricing)	ICER: no dynamic pricing	NR (no dynamic pricing)
Compliance	Post-acute period: Manufacturer: 93% CADTH: 100%	Manufacturer's value/assumption: RCT period: F/MF population • 6-11 years: 99.4% over 24 weeks • ≥12 years: 98.8% over 24 weeks RCT period: F/F population • 6-11 years: 100% over 24 weeks • ≥12 years: 99.7% over 24 weeks post-RCT period: F/MF and F/F population • 6-11 years: 80% • ≥12 years: 80% HAS: major limitation (see text)	NR	NR
monitoring costs	Liver function tests and ophthalmologist visits (no costs provided)	Liver function tests and ophthalmologist visits (no costs provided)	No additional costs above BSC	NR
Disease management costs	*Manufacturer* / *CADTH* Annual inpatient costs BSC • ppFEV1 ≥70%: CAD4136 / CAD4136 • ppFEV1 ≥40-69%: CAD7273 / CAD7273 • ppFEV1 <40%: CAD9600 / CAD9600 CFTR modulator • ppFEV1 ≥70%: CAD791 / CAD4136 • ppFEV1 ≥40-69%: CAD1382 / CAD7273 • ppFEV1 <40%: CAD1824 / CAD9600	Annual pathology follow-up costs: (incl. costs pulmonary exacerbations) children: • ppFEV1 ≥70%: €10 473 • ppFEV1 40-70%: €16 475 • ppFEV1 <40%: €26 919 adults: • ppFEV1 ≥70%: €17 337 • ppFEV1 40-70%: €31 438 • ppFEV1 <40%: €57 980	Disease management: • ppFEV1 ≥70%: $30 258 • ppFEV1 40-70%: $39 914 • ppFEV1 <40%: $68 240	NR

	Annual pharmacotherapy costs BSC • ppFEV1 ≥70%: CAD7834 • ppFEV1 ≥40-69%: CAD9280 • ppFEV1 <40%: CAD9562 CFTR modulator • ppFEV1 ≥70%: CAD6071 • ppFEV1 ≥40-69%: CAD7192 • ppFEV1 <40%: CAD7411	CAD7834 CAD9280 CAD9562 CAD7834 CAD9280 CAD9562			
Pulmonary exacerbations	NR		Annual costs pulmonary exacerbations: Children: F/MF & F/F population (weighted) • ppFEV1 ≥70%: €1542 • ppFEV1 40-70%: €1559 • ppFEV1 <40%: €1596 Adults: F/MF & F/F population (weighted) • ppFEV1 ≥70%: €1719 • ppFEV1 40-70%: €1746 • ppFEV1 <40%: €1803	Costs pulmonary exacerbations: age <18 years • ppFEV1 ≥70%: $63 204 • ppFEV1 40-70%: $100 143 • ppFEV1 <40%: $148 368 age ≥18 years • ppFEV1 ≥70%: $57 273 • ppFEV1 40-70%: $91 037 • ppFEV1 <40%: $130 460	NR
Lung transplant	NR		Lung transplant: NR Post-transplant costs: • year 1: €21 806 • year 2: €11 364 • year 3: €10 872 • year 4+: €9347	Lung transplant: $948 437 Post-transplant costs: • year 1: $365 773 • year 2+: $131 738	NR
Adverse events	NR		Sinusitis: €62.02 Headache: €73.33 Diarrhea: €86.85 Upper respiratory tract infection: €64.06 Abdominal pain: €86.85 Rash: €544 Increased ALT: €86.85 Nasal congestion: €62.02 Increased serum creatine kinase: €86.85 Increased AST: €86.85 Rhinorrea: €62.02 Rhinitis: €62.02 Cold (influenza): €62.02 Increased serum bilirubin: €86.85	NR	NR

Caregiver costs	NR	Caregiver cost weighted child/adult: • ppFEV1 ≥70%: €1826 • ppFEV1 40-70%: €2893 • ppFEV1 <40%: €4515	NR	NR

F/F: homozygous for F508del-CFTR; F/MF: heterozygous for F508del-CFTR with a minimal function mutation; IVA: ivacaftor (Kalydeco®); LUM-IVA: lumacaftor/ivacaftor (Orkambi®); NA: not applicable; NR: not reported; ppFEV1: percentage predicted forced expiratory volume in the first second; TEZ-IVA: tezacaftor/ivacaftor (Symkevi®/Symdeko®).

In the category of direct health care costs, adverse events (AEs) are also included in the CADTH and HAS analyses. In the CADTH report, it is mentioned that the cost of each adverse event was assumed to be equal to the cost of a single assessment by a general practitioner.[81] However, no further details are provided in the report. In the HAS report, a similar approach is applied and full details are provided. For BSC in the F/MF and F/F population, the information is based on study 109 (6-11 years) and study 102 (≥12 years). For Trikafta®, in the F/MF population, information is retrieved from study 116 (6-11 years) and study 102 (≥12 years). In the F/F population, this is study 106 (6-11 years) and study 106 (≥12 years). HAS made a minor remark stating that the safety data from the GALILEO study were not used to document the AEs of the BSC group alone in F/MF patients aged 6 to 11 years, even though these data were available.[62] In Table 16, an overview of costs related to AEs is provided. Table 17 presents the annual AE incidence rates by treatment and genotype as included in the HAS analysis. The AEs included occurred in at least 5% of patients in the Trikafta® group and were associated with an increase of at least 1% compared with the control group.[62]

In contrast with the CADTH and HAS analysis, no AEs were included in the ICER model. The assessors note serious and severe AEs were generally comparable across treatment groups and often higher in the placebo arms. Therefore, they did not explicitly model AEs in terms of added costs or disutilities.[5]

Table 17: Input data for annual AE incidence rates by treatment and genotype

	Patients 6-11 years			Patients ≥12 years		
	BSC (F/F & F/MF)	Trikafta® (F/F)	Trikafta® (F/MF)	BSC (F/F & F/MF)	Trikafta® (F/F)	Trikafta® (F/MF)
Headache	0.202	0.602	0.773	0.350	0.734	0.412
Upper respiratory infection	0.226	0.395	0.111	0.288	0.237	0.374
Abdominal pain	0.226	0.280	0.189	0.203	0.102	0.336
Diarrhoea	0.088	0.243	0.149	0.156	0.209	0.299
Skin rash	0.022	0.280	0.228	0.111	0.182	0.238
Increased ALT	0.202	0.243	0.189	0.077	0.155	0.226
Nasal congestion	0.179	0.356	0.111	0.168	0.155	0.214
Increased serum creatine kinase	0.000	0.067	0.036	0.099	0.102	0.214
Increased AST	0.156	0.067	0.111	0.044	0.128	0.214
Rhinorrhoea	0.110	0.280	0.269	0.066	0.076	0.190
Rhinitis	0.110	0.000	0.111	0.122	0.102	0.167
Flu	0.133	0.243	0.000	0.033	0.076	0.156
Sinusitis	0.088	0.033	0.000	0.088	0.050	0.121
Increased bilirubin	0.000	0.033	0.000	0.022	0.025	0.110

Source: HAS report.[62]

BSC: best supportive care; F/F: homozygous for F508del-CFTR; F/MF: heterozygous for F508del-CFTR with a minimal function mutation.

Finally, reference is made to non-health care costs, being caregiver and productivity costs:

– Caregiver costs:

  In the HAS report, the average hourly wage of a caregiver was used to calculate these costs. Similar to the included health care costs, these caregiver costs were split up according to ppFEV1 (see Table 16). In the ICER report, it was mentioned that any assumptions about how CFTR modulator drugs affect caregiver burden would be speculative.[5] They refer to a study by Neri et al.,[82] who found no relationship between caregiver burden, as measured by the General Strain Index, and patient factors such as ppFEV1 or occurrence of acute pulmonary exacerbations. As a result, they state that the addition of direct non-health care costs that are not affected by CFTR modulator treatments would result in an increase in total societal costs due to the substantial increase in life expectancy with modulator therapy.[5] Nevertheless, given the speculative nature of this impact, no impact on caregiver costs was included in the ICER analysis.

– Productivity costs:

  In the ICER report, for the societal perspective, an analysis provided by the CF Foundation regarding employment status among two groups of CF patients was used. Patients treated with Kalydeco® were matched with a group of patients who were not treated with a CFTR modulator. The analysis showed that treated patients were more likely to be employed full-time compared with untreated patients. Reported absolute differences in full-time employment varied from 3% among persons aged 18-24 years to 14.5% among persons aged 35-39 years.[5] The reported differences in the employment rates were used in the ICER report to incorporate the productivity gains associated with the CFTR modulators, assuming that they all had the same impact as observed with Kalydeco®. They used an average weekly wage of $971 (Bureau of Labor Statistics) plus a fringe rate. Furthermore, they also added productivity losses to the cost of acute pulmonary exacerbations.[5] In the end, because no substantial impact of treatment on indirect costs relative to direct health care costs was found, the ICER report presents the societal perspective as a scenario analysis and not as dual base-case analyses.[5]

7.2.2.5 Model input – effects

As mentioned in the CADTH report, ppFEV1, the annual number of pulmonary exacerbations, and weight-for-age z scores could be affected by treatment, and were updated every cycle, along with age. In the CADTH report, the key data for modelling the treatment effect was described as follows:[4]

– "Baseline patient characteristics were derived for each genotype separately from a number of trials of CFTR modulators in these populations."[4]

  The baseline characteristics were based on the following trials:[4]

  – F/F genotype: Study 011 Part B and Study 109[83, 84]

    Subset F/F patients from Study 106, Study 113, and Study 115[56, 85, 86]

  – F/MF genotype: Study 116 and subset of F/MF patients from Study 106[56, 87]

  – F/RF genotype: Subset F/RF patients from Study 113 and Study 115[85, 86]

  – F/G genotype: ENVISION, KONNECTION, KONDUCT[88-90]

– "Baseline mortality hazard was estimated based on an age-specific mortality from a CF population survival curve derived from the literature. This survival was adjusted for changes in clinical characteristics using a Cox proportional hazards model [see part 7.2.2.3].

– The manufacturer commissioned an indirect treatment comparison to inform placebo-adjusted estimates for acute change in ppFEV1 and mean change in weight-for-age z score in the F/F population for patients on CFTR modulators. Data for the F/MF population were based on Study 116, while the data for the F/RF and F/G populations were extrapolated from trial data for the population aged 12 years and older. Patients on BSC were assumed to not experience any increase in either outcome.

– Impact of treatment on long-term rate of decline in ppFEV1 was based on non-comparative literature and not specific to [Trikafta®]. Impact of CFTR modulator use on pulmonary exacerbations beyond the influences of changes in ppFEV1 to pulmonary exacerbation rates was based on an adjustment factor calculated by the [manufacturer]."[4]

In the CADTH analysis, patients on BSC alone were expected to not experience any acute increases in ppFEV1 or weight-for-age z score, and were assumed to experience a long-term decline in ppFEV1 in line with a study by Leung et al.[91] . The same rate of decline was applied to all genotypes, except the F/RF genotype, as it is typically associated with a milder form of disease and therefore a slower rate of decline.[4] A similar approach is followed in the HAS and ICER analyses. In the latter report, further details of the annual decline in ppFEV1 per age category are also provided (see Table 18). In the first stage of the model, no reduction in the rate of ppFEV1 (CADTH) or an increase in ppFEV1 in comparison to BSC (HAS and ICER) is assumed. In the second stage, a reduction in the rate of ppFEV1 decline is assumed of 80% (manufacturer) or 0% (CADTH),[4] 90%,[62] or 50%.[5] This wide variety of values for this reduction is based on the following assumptions:

– CADTH: The information was not available from clinical trials. "Based on registry-matched analyses, the reduction in rate of ppFEV1 decline for patients aged 6 to 11 years receiving LUM-IVA and IVA was assumed to be the same as that calculated for patients older than 12 years on each of these medications.[92] Data from Study 105 showed that patients receiving ELX-TEZ-IVA were assumed to experience a 96-week "maintenance period" during which their ppFEV1 did not decline at all after initial treatment.[41] Following this maintenance period, their lung function was assumed to decline, but at a rate of only 20% of the decline associated with BSC, based on registry data specific to TEZ-IVA and other assumptions."[4]

– HAS: The input is based on an indirect comparison, the validity of which could not be validated by the assessors. The assessors state that Trikafta® most strongly reduces the degradation of FEV1 (-90%) and that the choice to apply this reduction rate to all patients aged 6 and over, without this being demonstrated for part of the population, could be in favour of the product evaluated. The external validity of this approach could also not be checked.[62]

– ICER: three assumptions about the treatment effect after two years were modelled: "1) no ppFEV1 decline as long as the patient is on drug (favourable assumption), 2) no ppFEV1 decline on drug for 2 years and then a decline that is 50% of the standard care rate thereafter (plausible assumption), 3) no ppFEV1 decline on drug for 2 years and then a decline that is equal to the standard care rate thereafter (unfavourable assumption)."[5] The second assumption was used in the base-case analysis, arguing that 50% is in the range of the CFTR modulator effect on lung function decline.[93, 94] "[They] assumed that same long-term effect for all CFTR modulator drugs, even though they had different initial effects on ppFEV1. This was because of a lack of evidence on long-term effectiveness and because the estimates of decline with Kalydeco® and Orkambi® – two CFTR modulators with very different initial ppFEV1 effects – had very similar

long-term effect estimates (47% of standard of care rate for Kalydeco® and 42% of standard of care rate for Orkambi®).[94, 95 ”5]

Next to the treatment effect on ppFEV1, the CADTH and ICER report also include a separate treatment effect on pulmonary exacerbations. In the CADTH analysis, “the baseline rate of occurrence of pulmonary exacerbations each cycle was based on the patient’s ppFEV1 and age, according to a formula derived by Goss et al.[96] and was not genotype-specific. This rate was applied as derived by Goss et al. to all patients in the sponsor’s base-case analysis, which assessed patients 6 years of age and older, regardless of treatment received. Once patients turned 12 years old, the rate of pulmonary exacerbations for patients on CFTR modulators, including ELX-TEZ-IVA, was adjusted by a rate ratio derived by the sponsor.”[4] the CADTH assessors did not follow this approach and removed this additional impact. In the ICER model, the situation was even more complex. “The annual risk of having acute pulmonary exacerbation was modelled as a function of ppFEV1, age, and the number of acute pulmonary exacerbations the previous year.[96-98] Therefore, a hazard ratio for an increase in the rate of pulmonary exacerbations, depending on the number of exacerbations in the previous year, was added.”[5] As a result, a lower percentage of patients experiencing any exacerbations is modelled as well as fewer exacerbations among those who do experience at least one.[5]

In contrast, in the HAS analysis, it is assumed that there is no effect of the treatment on pulmonary exacerbations requiring IV antibiotics and/or hospitalization, because the pivotal trials carried out in this age group did not allow to estimate a rate ratio compared to untreated patients.[62] The assessors remarked that this was expected since pulmonary exacerbations occur less frequently in young patients. They assess the choice not to include a treatment effect on pulmonary exacerbations as conservative and acceptable.[62]

Table 18: Treatment effect included in the identified economic evaluations

	CADTH (2022)	HAS (2022)	ICER (2020)	INESSS* (2022)
ppFEV1	Reduction in rate of ppFEV1 during the first 96 weeks: none Reduction in rate of ppFEV1 decline with Trikafta® compared with BSC (after 96 weeks): Manufacturer: 80% CADTH: no reduction after 96 weeks	Increment in ppFEV1 Trikafta® vs placebo: F/MF population (GALILEO) • first 24 weeks: +11 F/F population (indirect comparison) • first 24 weeks: +13.9 Post-RCT period: 1) annual deterioration of FEV1: • age 6-12: -1.32 • age 13-17: -2.37 • age 18-24: -2.52 • 25+: -1.86 2) Reduction of FEV1 degradation: • BSC: 0% • Trikafta®: 90%	Annual decline in ppFEV1 • Age 6-8 years: -1.12 (-2.00 for F/F; F/G; or F/MF**) • Age 9-12 years: -2.39 • Age 13-17 years: -2.34 • Age 18-24 years: -1.92 • Age ≥25 years: -1.45 Increase in ppFEV1: F/F population: • Symdeko®: 4.0 (95%CI 3.1-4.8) • Trikafta® vs Symdeko®: 10.0 (no 95%CI) F/RF population • Trikafta®: 13.8 F/MF population • Trikafta®: 14.3 First two years: no reduction in ppFEV1	NR

			thereafter: 50% of the decline under standard care	
Pulmonary exacerbation	Pulmonary exacerbation rate ratio with Trikafta® compared to BSC: Manufacturer: 0.31 CADTH: 1.0	Age 6-11: no effect on pulmonary exacerbations	Annual rate of acute pulmonary exacerbation by age and ppFEV1: • Age <18 years: 8.5938*exp(-0.035*ppFEV1) • Age ≥18 years: 3.7885*exp(-0.026*ppFEV1) Acute pulmonary exacerbation RR: F/F population: • Symdeko®: 0.54 • Trikafta® vs Symdeko®: NR F/RF population • Trikafta®: NR F/MF population • Trikafta®: 0.37	NR
Lung transplant	patients with ppFEV1 <30% Probability lung transplantation: 11.3%	patients with ppFEV1 <30% Probability lung transplantation: • F/MF population: 51.2% (21/41) • F/F population: 47.3% (26/55)	patients with ppFEV1 ≤30% Probability lung transplantation: 64.7%	NR
Weight-for-age Z-score	NR	Increment weight-for-age z-score: F/MF population: • BSC: not applicable • Trikafta®: 6-11 years: +0.23 (24w) ≥12 years: +0.30 (24w) F/F population: • BSC: not applicable • Trikafta®: 6-11 years: +0.26 (24w) ≥12 years: +0.41 (24w)	Change in weight-for-age Z-score: F/MF and F/F population: 0.35 (0.20-0.51) F/RF population: 0	NR

BSC: best supportive care; ELX-TEZ-IVA: Trikafta®; NR: not reported; w: weeks.

F/F: homozygous for F508del-CFTR; F/G: heterozygous for F508del with a gating mutation; F/MF: heterozygous for F508del-CFTR with a minimal function mutation; F/RF: heterozygous for F508del-CFTR with a residual mutation.

* The input variables, values and assumptions are not transparently described in the INESSS HTA report. Therefore, no details could be included in the summary table. ** A higher decline for the youngest age group was assumed for individuals with these genotypes to fit trial-specific means.

All analysis included the possibility of receiving a lung transplantation for patients with ppFEV1 <30%, which was in line with guidelines.[99] The probability of receiving a lung transplantation varied widely: CADTH: the sponsor assumed that 11.3% of patients with a ppFEV1 under 30% would receive a lung transplant;[4] A separate mortality risk for patients following a lung transplant was also applied (no further details provided);[100] HAS: based on 2018 data from the French cystic fibrosis registry: in the F/MF population, among patients aged 6 years and older, 21 of 41 patients (51.2%) with FEV <30% had received a lung transplant. In the F/F population, this was 26 of 55 patients (47.3%);[62] ICER: Based on the study of Thabut et al.,[101] an annual risk of lung transplantation of 0.647 was assumed.[5]

Finally, the HAS and ICER analysis also included a treatment effect on the weight-for-age z-score. In the ICER report, it was assumed that the weight-for-age z-score was constant throughout life when patients did not receive CFTR modulator therapy, being -0.23.[102] It is noticed that the change in weight-for-age z-score reporting is variable and not consistent. It was assumed that all drugs would achieve the same effect on weight-for-age z-score as observed in the study of Borowitz et al.,[102]) with an exception for the F/RF population (see Table 18). In the ICER report, for the long-term horizon, it was assumed that the increase in weight-for-age z-score would persist lifelong.[94, 103] In the HAS report, the manufacturer referred to data from the GALILEO study to show that Trikafta® is associated with an increase in the weight-for-age z-score of 0.23 (95%CI 0.14-0.32) compared to baseline, adjusted for placebo, for the F/MF population.[62] For the F/F population, an increase of 0.26 (95%CI 0.14-0.37) was assumed based on an indirect comparison.[62] The HAS assessors criticized that in the GALILEO study, the weight-for-age z-score was not included in the primary or secondary endpoints. The absolute variation of the z-score was not subject to a correction for false-positive findings and was not presented in the results of the study provided by the manufacturer. As a result, they judged the hypothesis was not supported and could not be verified, which generated significant uncertainty.[62] Furthermore, according to the HAS assessors, the hypothesis of maintenance of the increase in weight over the entire time horizon was not sufficiently documented in the absence of long-term data available for this parameter.[62]

7.2.2.6 Model input – quality of life

The CADTH Canadian Drug Expert Committee (CDEC) discussed the impact of CF on patients and their caregivers, noting “the impact on health-related quality of life is particularly high and, as the disease progresses, the limitations on daily activities grow and more time and effort are needed to manage the progressive and debilitating symptoms. In addition to experiencing a physical decline, people with CF can also have psychological challenges, such as depression, anxiety, and hopelessness.”[64]

In the CADTH analysis,[4] in the absence of utilities based on a generic instrument (e.g., the EQ-5D (EuroQol 5-dimensions questionnaire)), the manufacturer used an equation developed by Solem et al. that included ppFEV1 and pulmonary exacerbations as predictors of an EQ-5D index utility score. For this calculation, each pulmonary exacerbation was assumed to last 21.7 days, based on the TRAFFIC and TRANSPORT trials.[104] No more specific information is available in this HTA report.

Also, the HAS report mentions that no EQ-5D data was collected in the Trikafta® trials. EQ-5D utility scores introduced into the model were linked to the FEV1 levels. The results of the study by Acaster et al.[105] presenting EQ-5D utility scores stratified by FEV1 level were applied as a baseline analysis (see Table 19).[62] This study was conducted in the UK in 401 patients aged 18 and over suffering from cystic fibrosis. It was designed to develop a mapping algorithm to estimate EQ-5D utility values from Cystic Fibrosis Questionnaire-Revised (CFQ-R) data. A decrement in utility is also associated with pulmonary exacerbations: -0.07 for 30 days.[62]

In the ICER report,[5] the linear interpolation of EQ-5D utilities by ppFEV1 conducted by Schechter et al. was used.[106] The disutility (-0.17) for experiencing an acute pulmonary exacerbation was applied for six months, referring to similar assumptions made by Tappenden et al..[107]

In the CADTH, HAS and INESSS reports, the manufacturer also included a treatment-specific utility increment for patients receiving Trikafta®. In the CADTH report, they argue that the equation by Solem et al.[104] did not capture the impact of treatment on non-respiratory outcomes. Therefore, an additional utility increment of 0.08 was modelled. None of the assessors followed this assumption. In a previous report of INESSS, it is noticed that the methodology detailing this increment is not very detailed and the hypothesis of a sustained long-term fixed effect is improbable.[108] According to the HAS assessors, the manufacturer's decision to add an incremental benefit to patients treated with Trikafta® is not acceptable. The manufacturer explains that this increment corresponds to the gain in quality of life 'unrelated to respiratory benefits', whereas HAS remarks the EQ-5D questionnaire already takes these benefits into account. The addition of this increment should at least have been discussed, especially as it is one of the most influential parameters in the model.[62] In the end, this additional increment is removed from all HTA analyses.

Post-lung transplant utilities were also included in the HTA analyses. CADTH refers to a study by Whiting et al.[97] without providing further details. In the HAS analysis, a post-transplant utility of 0.81 was applied.[62] In the ICER analysis, a much lower utility of 0.32 was used the first year after lung transplantation, referring to the study of Schechter et al.,[106] based on a quality of life (QoL) study for lung transplantation in patients with CF already published in 1994.[109] For the subsequent years after transplantation, the utility equivalent to a ppFEV1 of 70%-79% was applied (0.838).[5]

HAS also remarks there is no justification for not taking a utility decrement for AEs.[62] However, the CADTH report mentioned that no disutilities related to AEs were included in the model, as they were assumed to have minimal impact on patients' quality of life.[4]

Finally, the HAS assessors state that "in the context of a chronic disease where symptoms considerably alter patients' quality of life, and where one of the aims of treatment is to improve quality of life, a robust estimate of utility scores is essential."[62] Based on the above findings, such information is unfortunately lacking.

Table 19: Quality of life (utilities) included in the identified economic evaluations

	CADTH (2022)	HAS (2022)	ICER (2020)	INESSS (2022)
ppFEV1	NR	Utility scores: mean (SD) • ppFEV1 ≥70%: 0.74 (0.27) • ppFEV1 40-70%: 0.70 (0.26) • ppFEV1 <40%: 0.54 (0.29)	Utility values by level of ppFEV1: • >90%: 0.920 • 80-89%: 0.873 • 70-79%: 0.838 • 60-69%: 0.801 • 50-59%: 0.765 • 40-49%: 0.729 • 30-39%: 0.692 • 20-29%: 0.653 • <20%: 0.625	NR
Pulmonary exacerbation	Utilities: not reported Duration: 21.7 days	Utilities: -0.07 Duration: 30 days	Utilities: -0.17 Duration: 6 months	NR
Trikafta®	Manufacturer: +0.08 CADTH: no increment	Manufacturer: +0.0785 HAS: no increment	NR	Same as CADTH and HAS
Lung transplant	NR	Utilities post-transplant: • 0-6 months: 0.81 • 7-18 months: 0.81 • 19-36 months: 0.81 • ≥36 months: 0.81	Utilities post-transplant: • first year: 0.32 • subsequent years: 0.838	NR
Age-specific utilities	NA	NA	Age-specific utilities associated with aging population: • 0-9 years: 1.00 • 10-19 years: 0.950 • 20-29 years: 0.921 • 30-39 years: 0.906 • 40-49 years: 0.875 • 50-59 years: 0.849 • 60-69 years: 0.826 • 70-79 years: 0.787 • 80-89 years: 0.753 • ≥90 years: 0.725	NR

NA: not applied; NR: not reported; ppFEV1: percentage predicted forced expiratory volume in the first second; SD: standard deviation.

7.2.2.7 Uncertainty

In the CADTH, HAS and ICER report, deterministic and probabilistic sensitivity analyses are performed. No details are available for the INESSS report. CADTH also undertook a stepped analysis to highlight the impact of each change from the manufacturer's model. In the ICER report, a scenario analysis is performed assuming a start age of 6 years instead of 12 years for Trikafta® treatment, anticipating that younger patients would be eligible for this drug in the near future, which reflects our research question.

7.2.2.8 Results and conclusions

An overview of the results of the identified economic evaluations is provided in Table 20. We briefly present some of the main findings:

CADTH (2022):

– Based on the sponsor-submitted price for ELX-TEZ-IVA and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for ELX-TEZ-IVA compared with best supportive care (BSC) in patients aged 6 to 11 years was $1 434 435 per quality-adjusted life year (QALY) in the F/F genotype, $1 653 605 per QALY in the F/MF genotype, $2 437 481 per QALY in the F/RF genotype, and $1 531 443 in the F/G genotype.[4]

– In a scenario analysis assessing the cost-effectiveness of ELX-TEZ-IVA in patients 6 years and older, ICERs ranged from $1 129 990 to $1 868 095 per QALY compared with BSC.[4]

– The change to the sponsor's base case that had the greatest impact on the results was the removal of dynamic pricing due to the introduction of generic options, emphasizing the impact of drug acquisition costs as a key driver of the model. The next most impactful change was that in which the reduction in the rate of long-term ppFEV1 decline for CFTR modulators in comparison with BSC was removed.[4]

– ELX-TEZ-IVA was not cost-effective at a willingness-to-pay threshold of $50 000 per QALY in any scenario conducted by CADTH. A price reduction in excess of 90% for ELX-TEZ-IVA is required for all 4 genotypes for ELX-TEZ-IVA to be considered cost-effective at a willingness-to-pay threshold of $50 000 per QALY in comparison with BSC.[4]

HAS (2022):

– The manufacturer's base case for the F/MF population leads to an ICER of €495 596/QALY gained versus BSC over a 40-year time horizon. That is, 7 additional QALYs associated with Trikafta® versus BSC over 40 years for an additional cost of more than €3.4 million.[62]

– Comparing the results of the manufacturer with those of HAS is difficult since the base case analysis of HAS is not presented for the F/MF population, but for the F/F population. It leads to an ICER of €488 520/QALY gained versus BSC over a 40-year time horizon. That is, 7.2 additional QALYs associated with Trikafta® versus BSC over 40 years for an additional cost of more than €3.4 million.[62]

– The tornado graph of both the manufacturer's and HAS's analyses shows that post-trial compliance and utility by disease strata are the most influential variables for the intervention's cost-effectiveness.[62]

ICER (2020):

– The ICER for Trikafta® compared with BSC in patients aged 6 years was $1 262 000 per QALY gained in the F/F genotype, $1 139 000 per QALY gained in the F/MF genotype, and $1 164 000 per QALY gained in the F/RF genotype.[5]

– No further scenario analyses were performed for the scenario starting Trikafta® at the age of 6 years (since this was a scenario itself).

INESSS (2022):

– Although confidence in clinical inputs varies according to genotype, the INESSS does not consider it appropriate for this evaluation to separate the results into different types of analysis. The results of the analysis are therefore homogenised within a single ICER.[63]
– Following the changes made by the INESSS, the most likely average ICER is CAD1 082 650/QALY gained.[63]
– For the population of 6 years and older, the most likely average ICER for this population is $1 087 028/QALY gained. To achieve an ICUR of $50 000 and $100 000/QALY gained, a price discount of approximately 86% and 81%, respectively, is needed.[63]

Table 20: Incremental cost-effectiveness ratios presented in the identified economic evaluations

	Intervention comparator	Total costs	Incremental costs	Total LYs	LYG	Total QALYs	QALYs gained	ICER (currency/QALY)
CADTH (2022)	**F/F genotype**							
Sponsor's base case	BSC	CAD880 221		26.09		24.0		
	Trikafta®	CAD7 542 916	CAD6 662 694	39.64	13.55	38.8	14.76	CAD451 377
CADTH base case	BSC	CAD880 221		/		24.0		
	Trikafta®	CAD10 841 706	CAD9 961 485	/	/	31.0	6.9	**CAD1 434 435**
	F/MF genotype							
Sponsor's base case	BSC	CAD877 546		26.11		24.1		
	Trikafta®	CAD7 566 854	CAD6 689 307	39.53	13.42	38.7	14.66	CAD456 394
CADTH base case	BSC	CAD877 546		/		24.1		
	Trikafta®	CAD10 562 262	CAD9 684 715	/	/	29.9	5.9	**CAD1 653 605**
	F/RF genotype							
Sponsor's base case	BSC	CAD758 996		29.85		27.7		
	Trikafta®	CAD7 437 266	CAD6 678 270	38.74	8.89	38.0	10.27	CAD650 475
CADTH base case	BSC	CAD758 996		/		27.7		
	Trikafta®	CAD10 933 146	CAD10 174 150	/	/	31.9	4.2	**CAD2 437 481**
	F/G genotype							
Sponsor's base case	BSC	CAD986 009		25.96		23.8		
	Trikafta®	CAD7 541 447	CAD6 555 438	39.62	13.66	38.8	14.98	CAD437 639
CADTH base case	BSC	CAD986 009		/		23.8		
	Trikafta®	CAD10 630 705	CAD9 644 696	/	/	30.1	6.3	**CAD1 531 443**

HAS (2022)	**F/MF genotype**							
Sponsor's base case	BSC	€609 537		17.1		11.5		
	Trikafta®	€4 080 014	€3 470 477	23.2	6.1	18.5	7	€495 596
	F/F genotype							
HAS base case	BSC	€628 250		17.2		11.4		
	Trikafta®	€4 124 292	€3 496 042	23.4	6.2	18.6	7.2	**€488 520**
ICER (2020)	**F/F genotype**							
	BSC	$2 088 000		/		15.77		
	Trikafta®	$8 449 000	$6 361 000	/	/	20.81	5.04	**$1 262 000**
	F/MF genotype							
	BSC	$2 178 000		/		14.01		
	Trikafta®	$8 206 000	$6 028 000	/	/	19.3	5.29	**$1 139 000**
	F/RF genotype							
	BSC	$2 210 000		/		16.31		
	Trikafta®	$8 901 000	$6 691 000	/	/	22.06	5.75	**$1 164 000**
INESSS (2022)	**age 6-11 years**							
	BSC	/		/		NR		
	Trikafta®	/	CAD11 291 455	/	13.2	NR	10.4	**CAD1 082 650**
	≥6 years							
	BSC	/		/		NR		
	Trikafta®	/	CAD11 270 729	/	13.04	NR	10.37	**CAD1 087 028**

/: not reported; BSC: best supportive care; F/F: homozygous for F508del-CFTR; F/G: heterozygous for F508del with a gating mutation; F/MF: heterozygous for F508del-CFTR with a minimal function mutation; F/RF: heterozygous for F508del-CFTR with a residual mutation; LY(G): life year (gained); NR: not reported; QALY: quality-adjusted life-year

Table 21 provides an overview of conclusions as formulated in the identified HTA reports. The ICER report concluded that CFTR modulator therapies plus best supportive care substantially improve patient health outcomes compared to best supportive care.[5] However, the conclusions for the economic evaluations are less optimistic. Because of the high cost of these drugs, the cost-effectiveness of CFTR modulator therapies exceeds commonly used cost-effectiveness thresholds.[5] In the CADTH analyses,[4] Trikafta® price reductions of more than 90% are needed for all 4 genotypes for Trikafta® to be considered cost-effective at a willingness-to-pay threshold of $50 000 per QALY in comparison with BSC. In the HAS report, the assessors have major methodological reservations about the estimation of the utility scores and the relative efficacy estimates, invalidating the economic evaluation results.[62] Finally, also in the INESSS report, the price of Trikafta® is considered very high and unreasonable, and there are concerns about the long-term financial impact of this chronic treatment.[63]

Table 21: Conclusions formulated in the identified economic evaluations

CADTH (2022)	"Treatment with ELX-TEZ-IVA was not cost-effective at a willingness-to-pay threshold of $50 000 per QALY in any scenario conducted by CADTH. A price reduction in excess of 90% for ELX-TEZ-IVA is required for all 4 genotypes for ELX-TEZ-IVA to be considered cost-effective at a willingness-to-pay threshold of $50 000 per QALY in comparison with BSC."[4]
HAS (2022)	"The reference analysis proposed by the manufacturer does not demonstrate the efficacy of Kaftrio® in the population concerned by the request for reimbursement, due to major methodological reservations concerning the lack of documentation of the method used to estimate relative efficacy data for the homozygous population and the estimation of utility scores, which make it impossible to judge its admissibility."[62] "The efficacy of the product has not been demonstrated due to major reservations, invalidating the results of the economic evaluation. In fact, the lack of documentation concerning the indirect comparison carried out to estimate the relative efficacy data for the homozygous population makes it impossible to judge its acceptability. In addition, all the reservations and the conclusion expressed by the CEESP in its opinion of 9 February 2021 in the previous indication also apply to this dossier, including the major reservation concerning the estimation of utility scores. The results of the reference analysis cannot be retained."[62]
ICER (2020)	"We found that CFTR modulator therapies plus best supportive care substantially improves patient health outcomes compared to best supportive care. Because of the high cost of these drugs, however, the cost effectiveness of CFTR modulator therapies exceeds commonly used cost-effectiveness thresholds."[5]
INESSS (2022)	"The National Institute of Excellence in Health and Social Services (INESSS) recommends that the Minister include Trikafta® on the lists of medications for the treatment of cystic fibrosis (CF) in people aged 6 years or older, if the following conditions are met. … • Exceptional medicine; • Reducing the economic burden."[63] "The price of ELX/TEZ/IVA combination kits is still considered very high and unreasonable by members. Concerns were raised about the long-term financial impact, given that patients are likely to receive this treatment for the rest of their lives."[63]

CEESP: Commission de l'évaluation économique et de santé publique; CFTR: cystic fibrosis transmembrane conductance regulator; ELX/TEZ/IVA: elexacaftor-tezacaftor-ivacaftor

8. Methodology economic evaluation and budget impact analysis for Switzerland

8.1 Patient population

The population in this economic evaluation targets patients aged 6 and older with CF who have at least one F508del mutation in the CFTR gene. The systematic review of clinical evidence identified only one RCT in children aged 6 to 11 years. In this RCT, all patients had a minimal function mutation (F/MF), and a ppFEV$_1$ of at least 70%.[30] The other two identified RCTs included patients older than 12 years[31] or 18 years[29] and also focused on patients with F/MF. Only in the study of Keating et al.,[29] a small number of patients who were homozygous (F/F) for the *F508del* mutation were included, but these patients were randomized to a comparison that was not relevant to this report. The results for the homozygous patients (which were separately reported by the authors) were therefore not further considered in this report (see part 7.1.2.1). Given this evidence, the base case analysis focusses on patients with the F/MF mutation. We come back to this in the discussion.

8.2 Intervention and comparator

The intervention and comparator in the RCTs are Trikafta® and placebo. The Trikafta® dosage in the RCT of Mall et al.,[30] including 6-11 year old patients, reflects the dosage recommended by Swissmedic (see Table 2). The drug price is identified from the public database “Spezialitätenliste” by the Federal Office for Public Health (FOPH) (www.spezialitaetenliste.ch). Elexacaftor/tezacaftor/ivacaftor and ivacaftor are both oral drugs and are taken as tablets. In principle, patients are treated chronically.[24]

Trikafta® and placebo are given on top of best supportive care (BSC). Treatment consists of a combination of drugs aimed at controlling lung infections and inflammation (antibiotics), cystic mucus clearance (mucolytics) and improving nutritional status (pancreatic enzyme replacement therapy).[24]

Other CFTR modulators (Orkambi® and Symkevi®) are excluded, based on results of previous economic evaluations, due to extended dominance. We come back to this in the discussion.

8.3 Type of economic evaluation

The available RCTs and network meta-analysis provide consistent high-quality evidence for the effectiveness of Trikafta® in comparison with standard of care up to 24 weeks (see part 7.1). However, no generic utility instrument was used in the clinical studies. Notwithstanding, utilities were identified for different health states in the economic literature. Hence, it is chosen to perform a cost-utility analysis.

8.4 Perspective

The analysis is performed from a healthcare payers' perspective. Costs of healthcare services covered by the Swiss mandatory health insurance are analysed, irrespective of the actual payer (mandatory health insurer, other social insurer, government (federal government, cantons, communities) out-of-pocket). The analysis does not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs.

8.5 Time horizon

The time horizon usually reflects the period over which incremental costs and effects are generated. A model with a lifetime time horizon is constructed. However, given the limited maturity of the data in the clinical part (with most endpoints measured at about 4 or 24 weeks – see Table 9 and Table 10 in part 7.1.2.3) and the many assumptions made, results are presented for different time horizons (per 10 years) in scenario analyses.

8.6 Discount rate

Future costs and effects are discounted at 3% in the base case scenario. In sensitivity analyses, reflecting usual practice in Switzerland, discount rates of 0% and 5% are applied. In our economic evaluation, information is also retrieved from the Dutch ZIN report in which a differential discount rate of 4% for costs and 1.5% for effects is applied. In addition to the usual practice in Switzerland, a scenario with such an unequal discount rate is applied.

8.7 Modelling

8.7.1 Model structure

Previous models used a patient-level microsimulation model in which mortality was estimated based on a comparison with values for several variables (see part 7.2.2.3). Over time, patient characteristics evolved and mortality was calculated. Adjustment factors were applied to match the life expectancy targets of a CF cohort, without providing full details for all these variables and adjustments.

The studies refer to the original publication of Liou et al.[65] published in 2001. The objective of this US study was to create a 5-year survivorship model to identify key clinical features of cystic fibrosis. Multivariate logistic regression models were developed by using data on 5820 patients randomly selected from 11 630 patients from the Cystic Fibrosis Foundation Patient Registry (CFFPR) in 1993. The 5-year survivorship model included age, ppFEV1, gender, weight-for-age z score, pancreatic sufficiency, diabetes mellitus, Staphylococcus aureus infection, Burkerholderia cepacian infection, and annual number of acute pulmonary exacerbations. Infection with Burkerholderia cepacia had the largest effect of any model variable for predicting 5-year survivorship.[65]

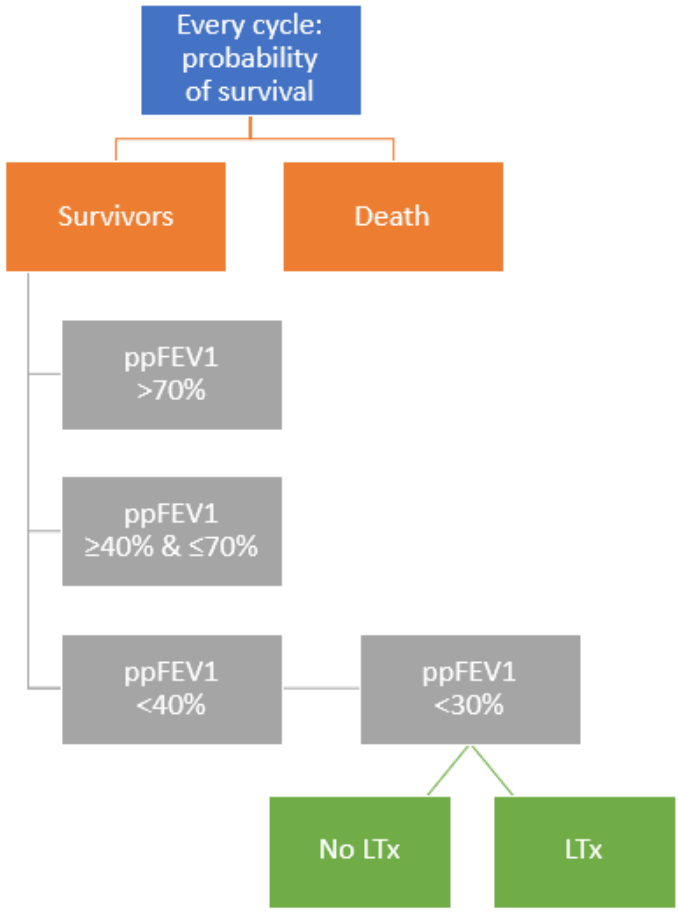
An Italian validation exercise of Buzzetti et al.[110] found a significant difference between observed and expected deaths based on Liou's model (62 vs 94), with a 34% reduction in mortality ($p<0.05$), and concluded the model did not adequately predict 5-year survival in their CF population. The authors mentioned that substantial improvements in therapeutic approaches and survival have occurred over the last decade,[110] which might be responsible for the difference between expected and observed deaths.

In 2020, Liou et al.[111] evaluated and modified their survival model based on data from four cohorts (1993–1998, 1999–2004, 2005–2010 and 2011–2016). Performance improved with the adjustment of the model intercept to account for overall improvements in mortality rates over time (confirming the findings of Buzzetti et al.). Liou et al. found that the predicted survival model in original and modified forms remained useful for disease categorization and individual prognosis.[111] Liou also performed a validation study together with the manufacturer. The modelled 5-year survival projections for people with CF initiating ivacaftor vs. standard care aligned closely with real-world registry data. They concluded these findings support the validity of modelling CF to predict long-term survival and estimate clinical and economic outcomes of CFTR modulators.[112]

The review of clinical evidence shows that there are currently no RCT-based results providing reliable evidence for the impact of Trikafta® on overall mortality, both in the short and the long term (see part 7.1.2.3). Predicting the long-term evolution of all variables in the risk prediction models, with the exception of e.g. gender and age, also involves large uncertainty. On top of that, there is also a high uncertainty about the long-term impact of Trikafta® on these variables. As the validation study of Buzzetti et al.[110] has shown, differences between predicted and observed deaths might be very significant.

To reflect this large uncertainty, we explicitly include a hypothetical treatment effect in different scenarios, modifying a hypothetical hazard ratio for the impact on survival over a wide range. Figure 10 describes the model structure. The assumptions regarding mortality, ppFEV1 and lung transplants are explained below.

Figure 10: Model structure



* LTx: lung transplantation; ppFEV1: percent predicted forced expiratory volume in 1 second.

8.7.1.1 Mortality

A Markov model is constructed with annual cycles in which mortality is initially modelled for the comparator group based on published survival curves. For this, we look at survival data from periods when CFTR-modulating therapies were not yet routinely used.[d] Annual cycles were chosen because the economic literature review showed most costs are expressed in yearly values (e.g. costs per ppFEV1 category or yearly costs after lung transplantation). In the model, a half-cycle correction is applied to account for the fact that events and transitions can occur at any point during the cycle, not necessarily at the start or end of each cycle (https://yhec.co.uk/glossary/half-cycle-correction/).

The extraction of points on the published survival curves was performed using the Datathief® software. For this, the figure is enlarged by 400% and the coordinate system is determined by indicating 3 points [origin (0,0); x-axis (0,100); y-axis (100,0)]. For each year, survival can be extracted from the figure and replicated in Excel. For the resulting survival curve, median and mean life expectancy can be calculated.

[d] The EMA date of authorization (www.ema.europa.eu) for Kalydeco®, Orkambi®, Symkevi® and Kaftrio® was 23/07/2012, 19/11/2015, 31/10/2018 and 21/8/2020, respectively.

For the survival in the intervention group, hazard ratios are applied via the following formula: probability of survival intervention group = probability of survival comparator group ^ (hazard ratio).

The different hazard ratios, decreasing in steps of 0.1, are applied side by side without any value judgement as there is no evidence to prefer one scenario over the other. It is verified that the annual mortality rate is not lower than that of the general Swiss population of the same age, which reflects that this population will not become healthier than the general Swiss population.[e] For the ages where there is no more survival in the comparison group (i.e. 72 and 85 years in the HAS and ZIN scenarios, respectively), the annual mortality rate increases with the absolute increase in the mortality rate of the same age-specific general Swiss population. The results are presented transparently by presenting the different simulated survival curves in a figure, calculating mean life expectancy, as well as displaying the impact of a change in mortality on IC, IE and the ICER in tables and a tornado graph. For the presentation of all further results, the scenario with a hypothetical hazard ratio of 0.1 is selected. This does not reflect a preference for this scenario but a practical consideration to be able to present all further scenarios for the other input variables.

8.7.1.2 ppFEV1

Initial value ppFEV1

A population of 1000 patients is modelled, reflecting the ppFEV1 of patients included in Study 116[30] with a probability distribution. This ppFEV1 was determined in study 116 at a mean age of 9 years. Through the annual estimated reduction in ppFEV1 (see next part), the ppFEV1 at the age of 6 years is calculated. This group of 1000 simulated patients is replicated so that the model starts with exactly the same patients at age 6 years in both the intervention and comparator group.

Evolution ppFEV1

The short-term impact of the intervention on ppFEV1 is modelled based on the evidence. Since no evidence exists for the longer term, the assumptions made in previous HTA reports are considered. The different scenarios are presented side by side.

8.7.1.3 Lung transplantation

According to practical guidelines for lung transplantation in patients with cystic fibrosis, prepared by a European working group, an FEV1 <30% of predicted values and/or a rapid decline in FEV1 despite optimal conservative treatment are two of the indicators that a pretransplant assessment is warranted.[113] In the identified economic evaluations, the possibility of lung transplantation was considered in patients with a ppFEV1 below 30% (see part 7.2.2.5). This possibility for lung transplantation is adopted in the model. The percentage receiving a lung transplant is based on

[e] A death rate for each age was calculated by dividing the number of deaths in 2022 obtained from Swiss life tables by the number of persons of that age in 2022. Sources: Swiss Federal Office of Statistic. Geburten und Todesfälle 2022, available from: https://www.bfs.admin.ch/bfs/de/home/statistiken/bevoelkerung/geburten-todesfaelle/todesfaelle.html accessed 2023/11/02. Swiss Federal Office of Statistic. Ständige und nichtständige Wohnbevölkerung 2022, available from: https://www.bfs.admin.ch/bfs/de/home/statistiken/bevoelkerung/stand-entwicklung.html, accessed 2023/11/02.

percentages used in the economic evaluations of previous HTA reports. Also here, the impact on the outcomes of the different scenarios will be presented.

Based on the above, surviving patients will be in one of the following health states:

– ppFEV1 ≥70%

– ppFEV1 ≥40% and <70%

– ppFEV1 ≥30% and <40%

– ppFEV1 <30% and did not receive a lung transplantation

– ppFEV1 <30% and received a lung transplantation

For the patients who received a lung transplantation, the model also tracks whether the surgery was performed 1, 2, 3, 4-10 or more than 10 years ago since quality of life (part 8.8.2) and costs (part 8.8.3) vary depending on whether a patient is in one of these categories. As such life years (gained), QALYs (gained) and incremental costs are calculated.

8.7.2 Model software and validity of the model

The model is set up in Excel. A Monte Carlo simulation Excel add-in (ModelRisk®, Vose Software) is used to include uncertainty in the model.

Several validity checks were carried out during the development of the model. The survival curves for the comparator group were copied from the original HTA reports from ZIN[24] and HAS[60] using Datathief® software. The reported and extracted 10- and 20-year survival (ZIN) and median survival (ZIN/HAS) were compared and are in agreement. The modelled life expectancy for the Swiss population in 2022 is 84.25 or 83.74 years, without or with inclusion of a half-cycle correction. This is in line with the published life expectancy at birth in Switzerland of around 84 years (source: https://www.oecdbetterlifeindex.org/countries/switzerland/ or https://data.oecd.org/healthstat/life-expectancy-at-birth.htm). Applying the Swiss-specific general probability of dying results in a modelled life expectancy for persons aged 6 years of 77.64 years, which is also in line with the expectations. The modelled survival curves for the intervention group are also visually checked in relation to the survival curve of the general Swiss population.

Next, the modelled utilities are compared across disease health states to check whether logical utility values are drawn from the probability distributions, i.e. utility (ppFEV1 ≥70%) > utility (ppFEV1 ≥40 to <70%) > utility (ppFEV1 <40%). We come back to this in part 8.8.2 and the discussion (part 10.2).

Backward calculation was done to check the formulas of the model in Excel.

Finally, it was checked whether the direction and magnitude of the impact of the different modelled scenarios were logical.

8.8 Input parameter

8.8.1 Clinical effectiveness

Table 22 provides an overview of the input variables used in the model to calculate the impact on mortality, ppFEV1, and the possibility of receiving a lung transplantation.

Table 22: Overview of input parameters in the (exploratory) economic evaluation

Input parameter	Base case estimate	Probability distribution	Source
Effectiveness			
Survival comparator group	Weibull survival curve Gompertz survival curve	NA	ZIN, 2021[24] HAS, 2021[60] See part 8.8.1.1
Treatment effect overall survival	Hazard ratio scenarios	NA	Hypothetical See part 8.8.1.2
ppFEV1 at 9 years	Mean: 87.2; range 55.8 to 119.6	Normal distribution with minimum and maximum limits	Placebo group Study 116[30] See part 8.8.1.3
Evolution ppFEV1 comparator group	According to age-specific categories (see Table 23)		See part 8.8.1.3
Evolution ppFEV1 intervention group	According to age-specific categories (see Table 24)		See part 8.8.1.3
Lung transplantation	52.4%	Beta distribution (55/105)	See part 8.8.1.4
Utilities			
ppFEV1 ≥70% ppFEV1 ≥40 to <70% ppFEV1 <40%	Mean 0.74 (SD 0.27) Mean 0.70 (SD 0.26) Mean 0.54 (SD 0.29)	Beta distribution	Acaster et al. (2015)[105]
1st year post-LTx ≥2nd year post-LTx	+0.1399 +0.1914	Beta distributions for underlying utilities	Bleisch et al. (2019)[114] See part 8.8.2

Costs			
Trikafta® treatment	CHF228 336 pp/py	Price discount scenarios	See part 8.8.3.1
Liver function test	CHF14.10 per determination	Fixed	See part 8.8.3.1
Eye examination	CHF190.30 per examination	Fixed	See part 8.8.3.1
Compliance 6-11y Compliance ≥12y	99.4% 98.8%		See part 8.8.3.1
Disease management costs Children (<18 years) • ppFEV1 ≥70%: • ppFEV1 40-70%: • ppFEV1 <40%: Adults (≥18 years) • ppFEV1 ≥70%: • ppFEV1 40-70%: • ppFEV1 <40%:	Base case (based on HAS report) CHF16 581 CHF26 083 CHF42 618 CHF27 448 CHF49 773 CHF91 794	Scenario analyses (based on CADTH and ZIN report) Uniform distribution (+/- 20%)	See part 8.8.3.2
Lung transplantation Procedure: Yearly follow-up cost: • 1st year: • 2nd year: • 3rd year: • year 4-10: • subsequent years:	Base case (based on Whiting report) CHF84 815 CHF43 669 CHF26 368 CHF27 720 CHF16 651 CHF9265	Scenario analyses (based on Swiss-specific costs for lung transplantation and information from the ZIN report) Uniform distribution (+/- 20%)	See part 8.8.3.3

LTx: lung transplant: NA: not applicable; pp/py: per patient per year; ppFEV1: percentage predicted forced expiratory volume in the first second; SD: standard deviation; y: years.

8.8.1.1 Mortality – comparator group

In the identified HTA reports, survival curves were not available by genotype. In the Dutch[24] and French[60] HTA reports, survival curves were published for a general CF population.

ZIN

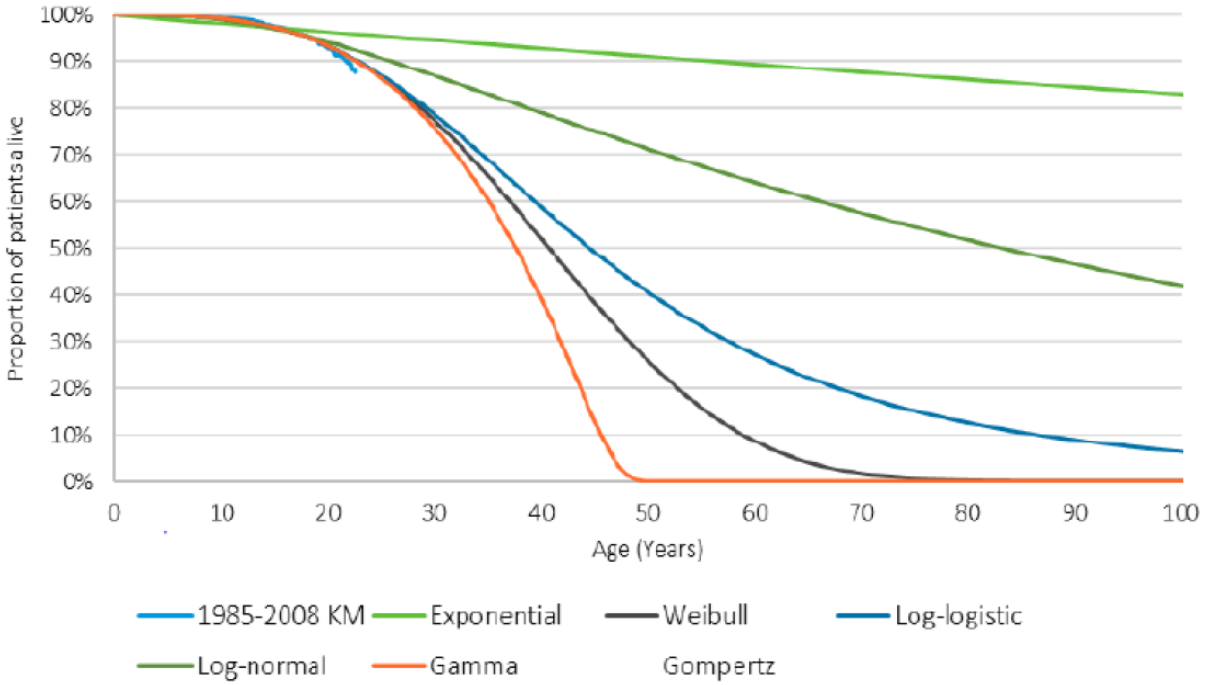
Given the relatively short duration of the Dutch CF registry (since 2008) and the relatively low number of deaths per year (10-20), the manufacturer indicated it was not possible to obtain reliable survival figures from the Dutch CF registry. However, survival figures were available from the UK and Ireland. For the Irish registry, it was indicated that survival in the group up to 20 years of age was only 83%, which was considered to be unrealistic by the manufacturer and a Dutch clinical expert. According to them, the UK registry had a more realistic survival of patients up to 20 years of age of 94%.

Complete survival data were not available in the UK CF registry. However, statistical distributions had been made from the observed data and future survival was estimated by extrapolating the survival curves. Different parametric distributions were tested and assessed for statistical fit, whether the fit was visually plausible relative to the observed data (KM curves), and whether the estimated survival was clinically plausible. It was assessed that the Weibull curve gave the best estimated survival with a median of 40.8 years.[24] In the Dutch HTA report, this curve was used in the base case analysis. The original survival curves presented in the ZIN report and the data from the Weibull curve, extracted via Datathief®, are presented in Figure 11.

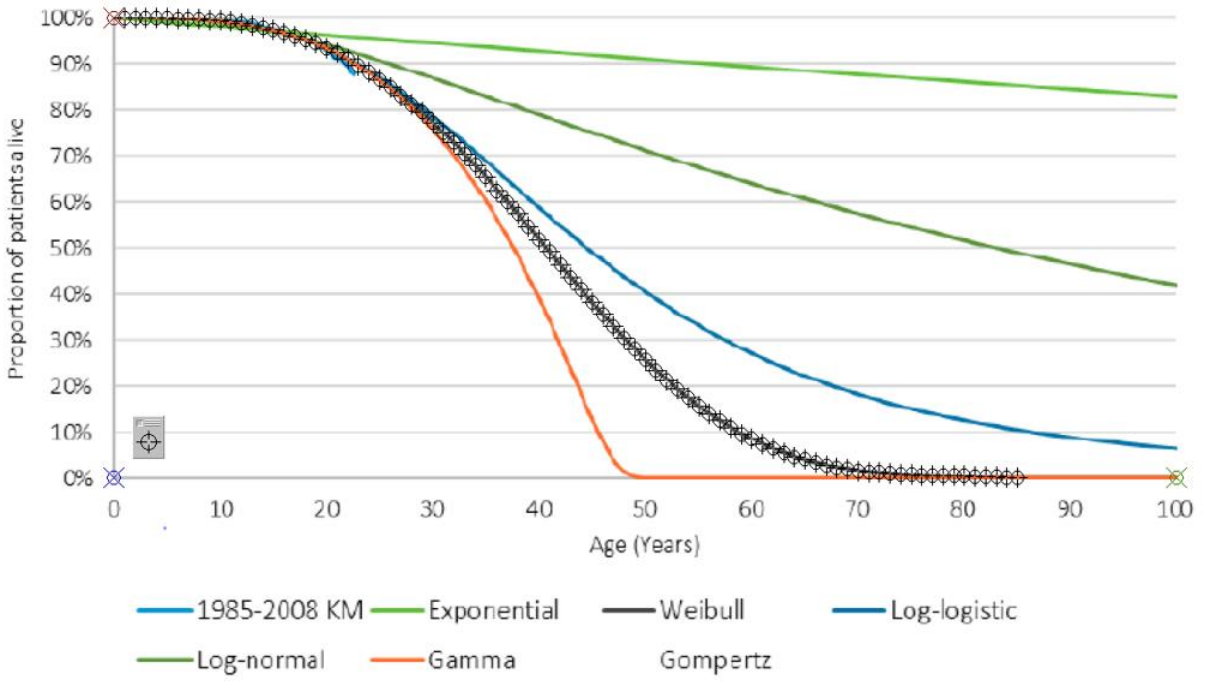
The data resulting from the extraction were verified by comparing them with the reported data: 99.5% versus ±99% (expected 10-year survival), 93.5% versus ±94% (expected 20-year survival) and 40-41 years versus 40.8 years (median survival) for Datathief® and the reported values, respectively.

Figure 11: KM curves ZIN report

a) Copy of figure from ZIN report*



b) Data extraction with Datathief®



* KM curve and parametric fits from the UK CF registry (all genotypes, birth cohorts 1985-2008). Source: Vertex, 2017[115]

HAS

In the HAS report, the mortality rate for each patient is estimated from the KM survival curve for the three birth cohorts of cystic fibrosis patients in the French register with a follow-up of more than 10 years: 1992-1996, 1997-2001 and 2002-2006. The maximum follow-up was 26, 21 and 16 years

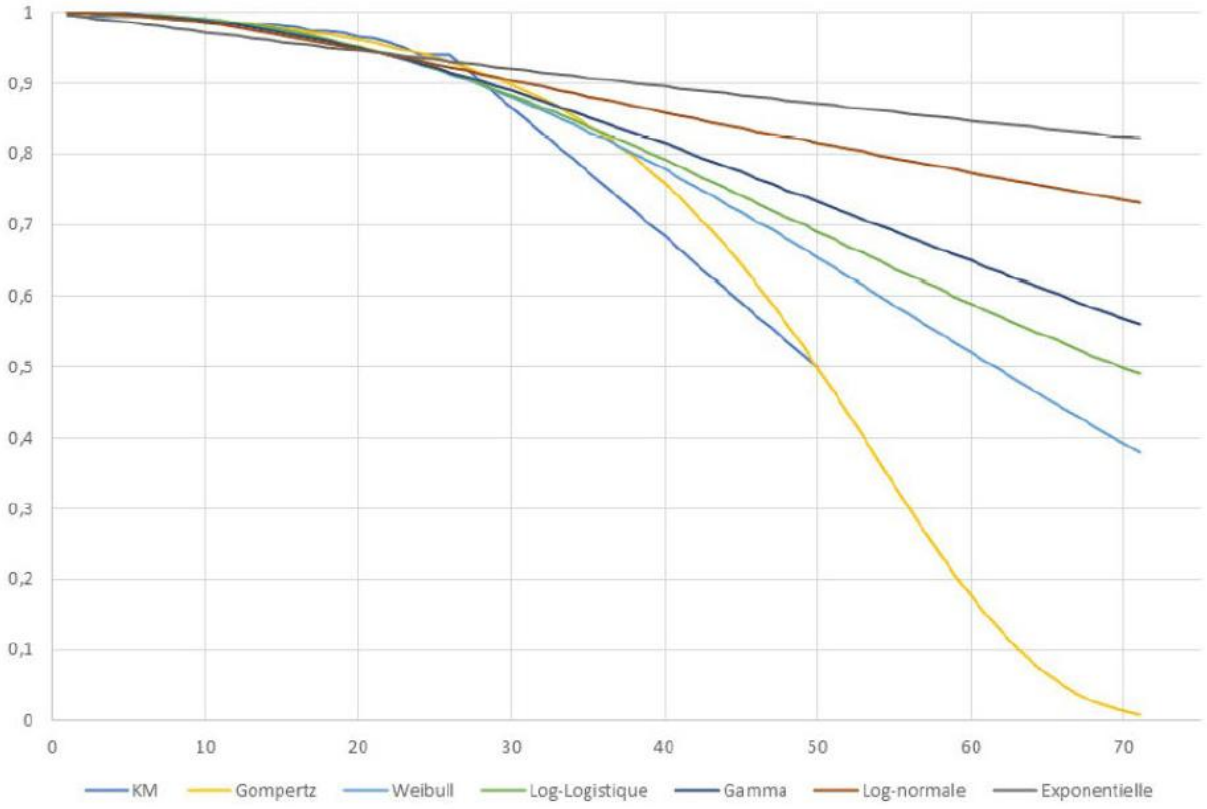
for the three cohorts, respectively. Survival rates were 87%, 95% and 98%, respectively. As the median survival rate was not reached over the observation period, a median survival of 50 years was chosen to facilitate extrapolation over a lifelong time horizon. This median survival was based on a study using data from the register. This study estimated the median survival of French cystic fibrosis patients to be between 57.6 and 49.3 years, depending on the applied method. The authors refer to a review by Scotet et al.[67] which supports this hypothesis, with an estimated median survival between 44 and 52 years in the United States, England, Ireland and Canada in 2018.

The KM curve completed by the median survival of 50 years was extrapolated using a parametric function, selected on the basis of the AIC and BIC criteria and the clinical plausibility of the curves obtained. The Gompertz function was selected for the reference analysis in the HAS report, simulating the extinction of the cohort at around 70 years of age.[60] The original survival curves presented in the HAS report and the extracted data from the Gompertz curve are presented in Figure 12.

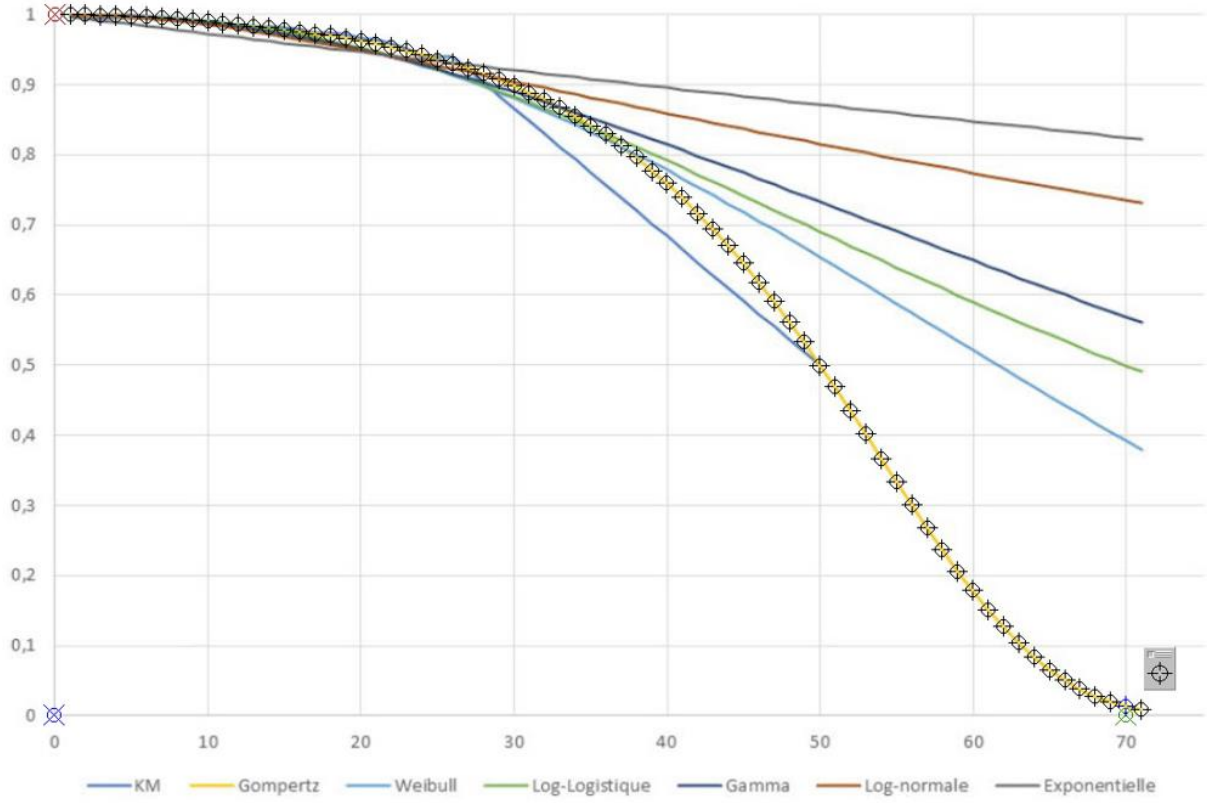
The data resulting from the extraction were verified by comparing them with the reported data: only the median survival was reported, which was both 50 years in the original graph and the extracted data.

Figure 12: KM curves HAS report

a) Copy of figure from HAS report* (x-axis: age; y-axis: proportion of patients alive)



b) Data extraction with Datathief® (x-axis: age; y-axis: proportion of patients alive)



* Different survival functions fitted to the data observed in the French cystic fibrosis register, with application of a median survival of 50 years. Source: HAS, 2021[60]

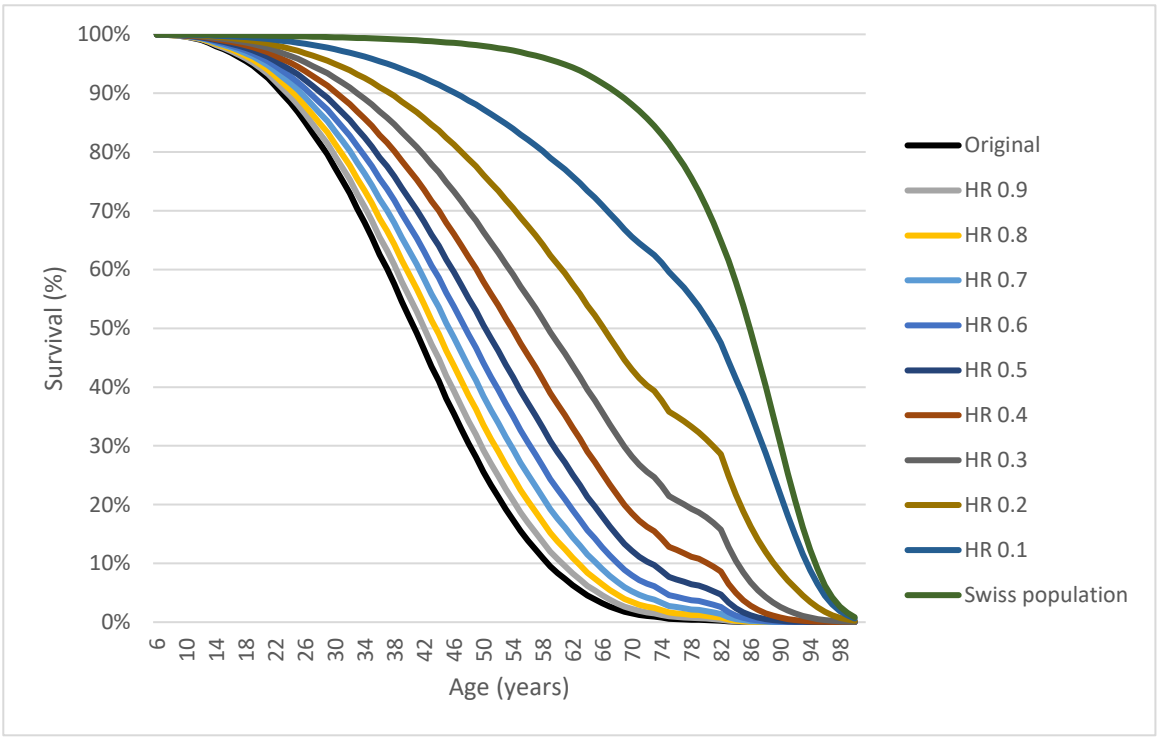
The above survival curves presented in the ZIN and HAS HTA reports start at birth. To reflect the inclusion criteria, a population of 1000 patients starting at the age of 6 years is modelled.

8.8.1.2 Mortality – intervention group

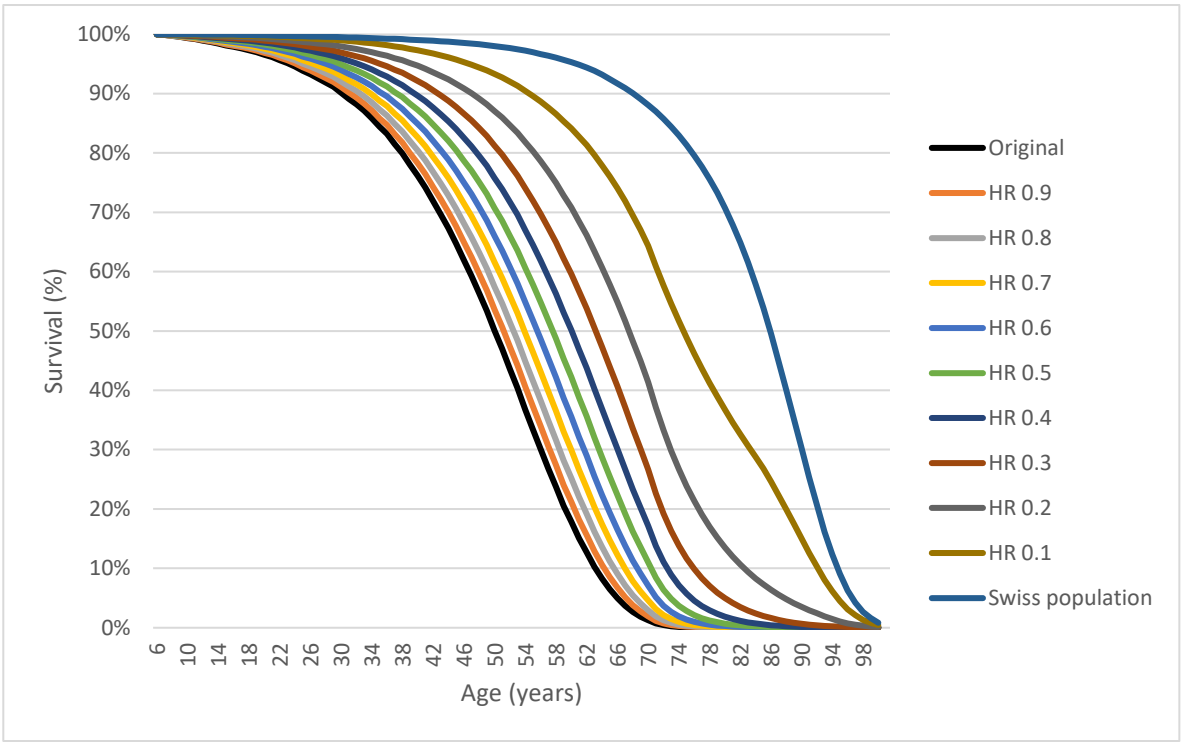
Figure 13 shows the resulting survival curves applying different hazard ratios, as explained in part 8.7.1.1.

Figure 13: Hypothetical survival curves for the intervention group

a) Hazard ratios applied to the original survival curve for the comparator group (ZIN report)



b) Hazard ratios applied to the original survival curve for the comparator group (HAS report)



HR: hazard ratio.

No separate impact on mortality is modelled for other events, such as exacerbations, lung transplantations and adverse events. Because of the high uncertainty about the magnitude of the impact on mortality, we preferred to model overall mortality and reflect the uncertainty about the impact on this outcome through the hazard ratio scenarios.

8.8.1.3 ppFEV1

For the surviving patients, the ppFEV1 is modelled. In study 116,[30] the mean age of patients in the comparator group (n=61) was 9.2 years and they had an average ppFEV1 at baseline of 87.2 (SD 15.8; median 89.6; range: 55.8 to 119.6). In a first step, the ppFEV1 values for 1000 patients were modelled using different probability distributions (normal and gamma distributions with and without limits). The normal distribution with minimum and maximum limits provided the best results in which not only the mean, but also the minimum and maximum values were reflected: after 1000 simulations, the average ppFEV1 was 87.2 (SD: 14.0; median 87.2; range 55.9 to 119.2).

In a second step, the ppFEV1 value in patients aged 9 years is transferred to the value at 6 years. This is done by applying the evolution in the decline of ppFEV1 without Trikafta®, as published in previous HTA reports. In the base case, the values are taken as presented in the HAS[62] and ZIN[24] reports (see Table 23). As an alternative scenario, the values presented in the ICER[5] report referring to the publication of Whiting et al.[97] are taken into account. As such, ppFEV1 is estimated at the age of 6 years, i.e. the starting age of the model.

The evolution of ppFEV1 in the comparator group is modelled as a function of patient age as shown in Table 23.

In the HAS analysis, a normal distribution was applied with a hypothetical 20% lower and upper limit. This results in a wider absolute range for variables with a higher baseline value. Instead, we preferred to model these variables as a beta-distribution with a standard deviation (SD) of 0.2% in absolute values. This results in an equal spread independent from the initial baseline value. The alpha and beta parameters of these beta distributions were determined for every input variable listed in Table 23. Without having an evidence-based preference, the HAS/ZIN input is used in the base case and the ICER/Whiting input is used in a scenario analysis.

Table 23: Evolution in ppFEV1 in the comparator group

	HAS/ZIN	ICER/Whiting	Probability distribution*
Age 6-8	-1.32%	-1.12%	Beta distribution with the same mean and a standard deviation of 0.2%
Age 9-12	-1.32%	-2.39%	
Age 13-17	-2.37%	-2.34%	
Age 18-21	-2.52%	-1.92%	
Age ≥25	-1.86%	-1.45%	

ppFEV1: percentage predicted forced expiratory volume in the first second.

* The alpha and beta parameters of the beta-distribution are determined in order to reflect the mean and a standard deviation of 0.2%.

An improved evolution in ppFEV1 is modelled for patients in the intervention group. Given the short follow-up of the trials, divergent assumptions were made in previous economic evaluations. We include the values as shown in Table 24. First, the ZIN report assumes a reduced decline for all age groups of 38.5%. Second, in the most optimistic scenario, the HAS report includes an absolute improvement of the ppFEV1 value of 11 (F/MF) or 13.9 (F/F) during the first 24 weeks. We modify this slightly by reducing the increase in ppFEV1 in the first year of our model until the mean is 100%,[f] which amounts to an improvement of 9.2. This corresponds roughly to the absolute change from baseline in $ppFEV_1$ through week 24 of 9.5 (95%CI: 6.6 to 12.4) in the Trikafta® group in Study 116.[30] After the first year, a reduction of 90% in the decrease of ppFEV1 was suggested by the manufacturer. Finally, the 'ICER plausible assumption' is also modelled in which there is no decline in ppFEV1 during the first two years, after which there is a 50% reduced decline of ppFEV1. The different assumptions will be presented as scenarios.

The ZIN and HAS scenarios presented in Table 24 are combined with the ZIN/HAS scenario presented in Table 23. Similarly, the ICER scenario presented in Table 24 is combined with the ICER/Whiting scenario presented in Table 23.

[f] A FEV1% of 100 means that the lung function measurement is equal to the mean lung function measurement of people of the same age, sex, and height of the healthy reference population. (Source: ECFSPR Annual Report 2021)

Table 24: Evolution in ppFEV1 in the intervention group

	ZIN	HAS	ICER	Probability distribution
Reduction in ppFEV1 decline	38.5%*	90%	50%	No probability distribution on the reduction in the decline
Age 6	-0.81%	Back to 100%**	0	
Age 7		-0.08%	0	
Age 8		-0.08%	-0.56%	
Age 9-12	-0.81%	-0.08%	-1.20%	
Age 13-17	-1.46%	-0.15%	-1.17%	
Age 18-21	-1.55%	-0.16%	-0.96%	
Age ≥25	-1.13%	-0.11%	-0.73%	

ppFEV1: percentage predicted forced expiratory volume in the first second.

* Remark: The ZIN report refers to a 61.5% reduction and requests to model a lower reduction of 47.5%. However, based on the data presented in the ZIN report, the reduction is initially 38.5% (for example: 1.32% x (1-0.385) = 0.81%, while 1.32% x (1-0.475) = 0.69%). We adopt the evolution in ppFEV1 in the ZIN scenario as published in the original report and as presented in this table. ** After 1000 simulations, this was an increase of ppFEV1 in the first year of on average 9.22 (95%CI: 8.09 – 10.18).

8.8.1.4 Lung transplantation

The previously published economic evaluations assume that in case a patient's ppFEV1 declines below 30%, the patient is eligible for lung transplantation. The Dutch report refers to a study of Liou et al.[65] indicating that a patient mainly benefits from a lung transplant if the ppFEV1 is less than 30%. It is also noted that whether the patient who qualifies for a lung transplant actually receives one depends on several factors, which are not included in the models, such as meeting waiting list requirements and the availability of a donor organ.[24]

As noticed in the economic literature review, the percentage that effectively received a lung transplant varied widely across previous economic evaluations. The yearly reports of the transplantation centre of the University Hospital Zurich provided Swiss-specific information. In 2021, with regard to lung transplants, the Transplantation Immunology Laboratory carried out 57 transplant immunology analyses of potential recipients, and 24 patients received a new lung at the University Hospital Zurich.[116] In 2022, 48 immunological transplant evaluations of potential candidates were carried out and 31 patients received a new lung at the University Hospital Zurich.[117] Combining the numbers from these two most recent years, we took into account an average of 52.4% (55/105) of

patients receiving a lung transplant in the model. This reflects the percentages mentioned in the ZIN[24] (47.3%) and HAS (F/MF: 51.2%; F/F: 47.3%) reports.

As scenario analyses, the lowest number of 11.3%[4] and the highest number of 64.7%[5] from previous HTA reports is taken into account to see how this impacts cost-effectiveness calculations (Table 25).

Finally, in the ZIN report,[24] the assumption is made that if the patient did not receive the lung transplant in the cycle they are eligible for this, there will also be no lung transplant in a later cycle. This assumption is adopted in the economic model.

Table 25: Percentage of eligible patients receiving a lung transplant

	Mean	Probability distribution
Base case	52.4%	Beta distribution (55/105)
Scenario analyses	11.3% - 64.7%	NA

NA: not applied.

8.8.2 Utility

The economic literature review showed that the HAS and ICER model included utilities for different ppFEV1 categories (see Table 19 in part 7.2.2.6). The ZIN report used the same approach as in the HAS report, applying the utility values based on the study from Acaster et al.[105] We follow the same approach.

In the UK study of Acaster et al.,[105] 401 adults with cystic fibrosis completed a survey in which the EQ-5D-3L (EuroQol 5-dimensions 3-level) questionnaire was included. The utility values for mild (>70%), moderate (>40% and ≤70%) and severe (≤40%) FEV1 were as follows: 0.74 (SD 0.27); 0.70 (SD 0.26) and 0.54 (SD 0.29), respectively. Initially, we modelled these three utilities as a beta distribution with the reported standard deviation. However, the standard deviation of these utilities is very large. When performing 1000 independent simulations for the three utilities, the utilities are not in the correct order: i.e. in about 2/3 of the simulations, the utility of a worse health state is better than the utility of a better health state: i.e. utility (ppFEV1 ≥70%) < utility (ppFEV1 ≥40 to <70%) OR utility (ppFEV1 ≥40 to <70%) < utility (ppFEV1 <40%). To make sure that only logical utility values are drawn, the standard deviation was divided by ten and a correlation was included between the utility values of the mild and moderate FEV1 categories. This results in simulations where utility (ppFEV1 ≥70%) > utility (ppFEV1 ≥40 to <70%) > utility (ppFEV1 <40%). We come back to this in the discussion (see Figure 30).

The ICER report refers to a linear interpolation of EQ-5D utilities by ppFEV1 conducted by Schechter et al.,[106] based on EQ-5D values estimated for ppFEV1 groups among CF patients that were provided to Tappenden et al.[107] for a NICE economic evaluation. This study refers to the study of Bradley et al.[118] to estimate EQ-5D based on ppFEV1% in patients with CF. The study of

Bradley et al.[118] only published EQ-5D scores according to the severity of pulmonary exacerbations: patients with more severe pulmonary exacerbations have poorer HRQoL. EQ-5D utility index means were 0.85 (95% CI: 0.80–0.89), 0.79 (95% CI: 0.67–0.91) and 0.60 (95% CI: 0.44–0.76) for no, mild and severe pulmonary exacerbations, respectively. Although we could not identify the data in the original reference, the study of Tappenden et al.[107] includes the following utilities: ppFEV1 ≥70%: 0.86 (SD 0.03); ppFEV1 ≥40 to <70%: 0.81 (SD 0.04); and ppFEV1 <40%: 0.64 (0.06). We apply these values in a scenario analysis. Also in this case, a correlation was included between the utility values of the mild and moderate FEV1 categories to avoid illogical values in the 1000 simulations.

In previous economic evaluations, another disutility was modelled separately for pulmonary exacerbations, with an impact lasting about 3 weeks to 6 months (see part 7.2.2.6). However, the study by Acaster et al. shows in the patient characteristics that 114 (30.1%) of the patients recently had an exacerbation. Of this group, 42 (36.8%) patients were hospitalised for this purpose.[105] Thus, the results of this study are already influenced by the occurrence of exacerbations. People with a worse ppFEV1 value have a higher probability of being confronted with exacerbations and a worse QoL is already reflected for the different ppFEV1 categories. To avoid double counting, we decided not to model exacerbations separately and not to add an additional disutility to the model.

The manufacturer also included a utility increment of 0.08 related to the use of Trikafta®,[4, 24, 62] independent from the impact on the ppFEV1 categories. The manufacturer's argument is that patients receiving Trikafta® also showed improvements in multiple non-respiratory domains of the CFQ-R questionnaire, such as physical and social functioning, health perceptions and vitality.[31, 34] As reflected in the ZIN report, all domains of the CFQ-R are already included in the EQ-5D. The assessors of the CADTH and HAS report also disagree with this increment. In line with these previous assessments, we are also of the opinion that the inclusion of an additional incremental utility leads to double counting in Trikafta®'s favour. An additional incremental utility for the use of Trikafta® is therefore not included in the model.

Patients undergoing lung transplantation experience an impact on their quality of life. Based on a targeted non-systematic search strategy, the publication by Bleisch et al.[114] was identified. This publication presents an HRQoL analysis of the Swiss Transplant Cohort Study of lung transplant recipients with a follow-up of three years. This prospective study presents the evolution in QoL of 27 lung transplant recipients, using the EQ-5D-3L questionnaire. The authors find that lung transplant recipients show the most pronounced improvements in HRQoL and reduction in psychological distress between two weeks and three months post-transplant, with relatively stable HRQoL and distress trajectories thereafter.[114] The mean QoL was 0.70 (SD 0.18) before transplantation. This decreased to 0.62 (0.26) two weeks post-transplant, and already increased to 0.85 (0.15) three months post-transplant (see Table 26). After 6 months and 3 years, utilities remained relatively stable at 0.87 (0.13) and 0.90 (0.12), respectively.

We did not apply these utilities directly to the population receiving a lung transplant because of the large difference in the utilities in the pre-transplant period: in the study of Bleisch et al., the utility in the pre-transplant period was 0.70, while in the study of Acaster et al., the population with a ppFEV1 <40% had a utility of 0.54. Therefore, we use the incremental evolution in QoL in lung transplant patients. To calculate the utility value for the first year, we use a linear improvement in QoL between the published utility for the first, third, and sixth months and the assumed utility for month 12. For the utility value in the 12th month, we assumed the same value as reported for the 3rd year. As such, an average utility increase of 13.99 was obtained for the first year and 19.14 in subsequent years (see Table 26).

Due to a lack of information on the impact on QoL related to AEs (see part 7.2.2.6), no such adjustment is taken into account in the model.

Table 26: Utilities applied to different health states

Health state	Base case estimate mean (SD)	Probability distribution	Source
Trikafta® treatment	No utility increment		
ppFEV1 ≥70%	0.74 (~~0.27~~) (adjusted SD 0.027) Scenario: 0.86 (0.03)	Beta distribution	Acaster et al. (2015)[105] (HAS[62] and ZIN[24] report) Scenario analysis: Tappenden et al.[107]
ppFEV1 ≥40 to <70%	0.70 (~~0.26~~) (adjusted SD 0.026) Scenario: 0.81 (0.04)	Beta distribution	
ppFEV1 <40%	0.54 (~~0.29~~) (adjusted SD 0.029) Scenario: 0.64 (0.06)	Beta distribution	
Pre-transplant	0.7043 (0.1770)		Bleisch et al. (2019)[114]
Post-transplant QoL:			
Week 2 (1st month)	0.6217 (0.2575)		
Month 3	0.8522 (0.1504)		
Month 6	0.8739 (0.1322)		
…Year 3	0.8957 (0.1224)		
Incremental:			
1st year post-LTx	+0.1399	Fixed value	
≥2nd year post-LTx	+0.1914	Fixed value	

LTx: lung transplantation; ppFEV1: percentage predicted forced expiratory volume in the first second; QoL: quality of life; SD: standard deviation.

8.8.3 Costs

Costs associated with Trikafta® treatment, or costs associated with cystic fibrosis potentially affected by the use of Trikafta®, are identified and valued. Resource utilisation data and/or cost information are informed by peer-reviewed or grey literature sources, with a preference for Swiss-specific sources. In case such information is lacking, cost information from the identified economic evaluations will be converted to Swiss costs (CHF) by applying purchasing power parities (PPP) and consumer price indices (CPI) adjustments (source: https://stats.oecd.org).

Where possible, cost information is gathered for the year 2023. However, the most recent conversion factors (PPP and CPI) are published for the year 2022. As a result, cost information is expressed in CHF for the year 2022/2023.

Swiss-specific cost data are sourced from the Spezialitätenliste for medicine costs, the Swiss diagnosis-related group (DRG) costs for inpatient services, and the Analysenliste for laboratory costs.

8.8.3.1 Trikafta® treatment

The recommended dosage and resulting yearly costs for Trikafta® treatment are shown in Table 27 and Table 28. Half of the dosage is given to children under 12 years of age who weigh less than 30kg (Table 27). However, the price for half-dose tablets is exactly the same as the price for the dose given to adults or children weighing more than 30kg (Table 28). This results in an annual cost of CHF228 336 per patient.

It is possible that in practice the cost may be lower than the official list price because of a confidential price agreement. In the report, the official list price is applied and price discounts in steps of 10% are applied in scenario analyses.

Table 27: Trikafta® treatment – recommended dosage

Age (weight)	Morning dose (2 tablets)	Evening dose (1 tablet)
6-<12 years (<30kg)	Elexacaftor 50 mg, tezacaftor 25 mg, and ivacaftor 37.5 mg	Ivacaftor 75 mg
6-<12 years (≥30kg)	Elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg	Ivacaftor 150 mg
≥12 years	Elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg	Ivacaftor 150 mg

Table 28: Trikafta® treatment – price information

Content	Public price (incl.VAT)	Price per day*	Price per year
84 tablets: • 56 tablets elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg • 28 tablets ivacaftor 150 mg	CHF17 516.15	CHF625.58	CHF228 336
84 tablets: • 56 tablets elexacaftor 50 mg, tezacaftor 25 mg, and ivacaftor 37.5 mg • 28 tablets ivacaftor 75 mg	CHF17 516.15	CHF625.58	CHF228 336

VAT: value added tax.

Source: "Spezialitätenliste" (www.spezialitaetenliste.ch). * see recommended dosage in Table 27.

The summary of product characteristics mentions the "assessments of transaminases (ALT and AST) and total bilirubin are recommended for all patients prior to initiating treatment, every 3 months during the first year of treatment and annually thereafter."[119] Furthermore, a "doctor may do eye examinations before and during treatment with Kaftrio®. Cloudiness of the eye lens (cataract) without any effect on vision has occurred in some children and adolescents receiving this treatment."[119] In line with this information, additional costs of liver function tests and eye examinations are applied to patients treated with Trikafta® (Table 29). These costs are included as fixed costs in the economic model.

Table 29: Trikafta® treatment – costs of liver function tests and eye examinations

	Quantity	Price	Source
Liver function test	1st year: 4 times Afterwards: yearly	CHF14.10 per determination*	Swiss expert
Eye examination	1st year: 2 times	CHF190.30 per examination**	Swiss expert

* Liver function tests (AST, ALT): ALT: Item 1020.00 / 2.3 tax points plus suffix C surcharge item 4707.10 of 1.8 TP. AST: item 1093.00 / 2.3 tax points plus suffix C surcharge item 4707.10 of 1.8 TP. Blood sampling by the laboratory: item 4701.00 / 5.9 TP. The tax point is charged at CHF1.00 for outpatients. ALT and AST together therefore cost CHF8.20. Together with the blood sampling, this costs CHF14.10 per determination.

** Based on an ophthalmologist's examination (fundus background, lens assessment, etc.) in the eastern part of Switzerland. An ophthalmological examination should be carried out twice: once before the start of Trikafta® therapy and once approximately three months after the start of therapy. Later only if symptoms occur.

It is assumed that all patients are treated chronically.[24] The ZIN report assumes a 99.7% and 98.8% adherence after 24 weeks for the F/F and F/MF populations, respectively. This is close to the 100% assumed in the HAS report (see part 7.2.2.4). As in the CADTH and HAS report, the manufacturer also assumed lower compliance of 88% in the post-RCT period in the ZIN report. However, in line with the CADTH and HAS assessors, ZIN does not agree with counting lower costs due to lower compliance, but not including lower efficacy linked to this reduced compliance. In line with previous HTA assessors, we follow this argument and keep compliance at the same level. In the model, compliance is assumed to be 99.4%[62] for patients 6-11 years old and 98.8% for patients ≥12 years old and this for the entire duration of the model. Patients receiving lung transplant stop Trikafta® treatment.

In the identified economic evaluations, with the exception of the HAS evaluation, no adverse event related specific costs were reported (see Table 16). In the CADTH report, the cost of each adverse event was assumed to be equal to the cost of a single assessment by a general practitioner.[120] In the ICER report, it was indicated that "serious and severe AEs were generally comparable across treatment groups and often higher in the placebo arms. Therefore, [they] did not explicitly model AEs in terms of added costs or disutilities but assumed that patients who experienced a bothersome AE would discontinue the drug. As the discontinuation rates typically reported in the trials were greater than the reported discontinuation rates due to AEs, [they] assumed that the reported discontinuation rates included discontinuation due to AEs."[5] Furthermore, in the ZIN report, an expert consulted by the manufacturer indicated that the costs of adverse events were already included in the disease management costs. To avoid double-counting, these costs were not included separately. In line with these arguments, no separate AE-related costs were included in the intervention or comparator group. Only general disease management costs linked to ppFEV1 were included (see part 8.8.3.2).

8.8.3.2 Costs related to ppFEV1

In a non-systematic literature search for Swiss-specific cost information, the following report was identified: "Direct medical costs of cystic fibrosis in Switzerland" (source: https://www.zhaw.ch/en/research/research-database/project-detailview/projektid/6130/). The description mentions "the objective of the study is to estimate the annual direct medical costs related to the treatment of CF patients in Switzerland from a health care payer perspective using a prevalence-based bottom-up approach." While the project status indicates the project is completed, no full report could be identified (Website accessed in September and November 2023). The project leader was contacted end of September. Unfortunately, no publication was yet available.

Swiss-specific costs were received from the FOPH related to pulmonary exacerbations: 'DRG E60A - Zystische Fibrose (Mukoviszidose) oder andere Lungenerkrankungen mit Evaluation zur Transplantation oder Alter < 16 Jahre' and 'DRG E60B - Zystische Fibrose (Mukoviszidose) ohne andere Lungenerkrankungen mit Evaluation zur Transplantation oder ARDS, Alter > 15 Jahre, mehr als ein Belegungstag', with an average cost of CHF21 568 or CHF15 167, respectively. However, only

including these costs would underestimate the disease management costs since these also include non-exacerbation-related costs. As a second-best alternative, cost information from previous HTA reports was applied in scenario analyses. In the economic literature review, costs were split according to the ppFEV1 category (see part 7.2.2.4).

Purchasing power parities were applied to switch from foreign currencies to CHF. To express costs in the most recent year, the consumer price index was applied. The US study was excluded because of the non-applicability of US costs to the Swiss setting. The information from the French, Canadian and Dutch studies were retained.

As in the Canadian study, the manufacturer in the Dutch study assumes a lower cost for the different ppFEV1 categories if a CFTR modulator is used. To support this, they refer to lower hospital admissions[77] and less antibiotic use.[76] However, the ZIN assessors report that there is no evidence of a decrease in drug costs with CFTR therapy. Their real-world data show that the number of daily defined doses used per user of dornase alfa, which is a major component in drug costs, has not decreased significantly over the past 5 years.[121] At the request of the ZIN assessors, a scenario was added in their analysis in which there is no cost-reduction associated with using the CFTR modulators. There are arguments both in favour and disfavour for using equal or unequal costs within each ppFEV1 category. In this report, the costs from the HAS report are included in the base case in which there is no additional cost benefit for CFTR modulators within each ppFEV1 category. In scenario analyses, the costs from the CADTH and ZIN reports are modelled, applying both a scenario without and with the cost benefit for CFTR modulators within each ppFEV1 category. We note that the details reported in the HAS and ZIN reports make it clear that exacerbation-related costs are included in the disease management costs. Hence, these costs are not modelled separately, which would lead to double counting.

As mentioned in the previous section, costs of adverse events are assumed to be included in the disease management costs[24] and are therefore not modelled separately.

Table 30 shows the costs used, as well as the adjustment via PPP and CPI to convert the costs from the HAS, CADTH and ZIN reports to CHF for the year 2022.

Given the lack of further information about the confidence interval surrounding these costs, a uniform distribution with a minimum and a maximum of +/- 20% is applied to these costs.

Table 30: Disease management costs (unadjusted and adjusted to CHF, 2022)

	HAS		CADTH*		ZIN**	
Unadjusted:	Children (<18 years)	Adults (≥18 years)	BSC & CFTR***	Lower CFTR****	BSC & CFTR***	Lower CFTR****
• ppFEV1 ≥70%:	€10 473	€17 337	CAD11 970	CAD6862	€9750	€8114
• ppFEV1 40-70%:	€16 475	€31 438	CAD16 553	CAD8574	€22 535	€17 367
• ppFEV1 <40%:	€26 919	€57 980	CAD19 162	CAD9235	€50 663	€40 917
Currency and year of costing	€, 2021		CAD, 2021 (not reported§)		€, 2015	
Adjustment:	Multiplication factor:		Multiplication factor:		Multiplication factor:	
• to CHF via PPP:#	x 1.5396		x 0.8936		x 1.5257	
• to 2022 via CPI:&	x 1.0284		x 1.0284		x 1.0412	
• combined:	x 1.5832		x 0.9189		x 1.5886	
Adjusted costs:	Children (<18 years)	Adults (≥18 years)	BSC & CFTR***	Lower CFTR****	BSC & CFTR***	Lower CFTR****
• ppFEV1 ≥70%:	CHF16 581	CHF27 448	CHF11 000	CHF6306	CHF15 489	CHF12 890
• ppFEV1 40-70%:	CHF26 083	CHF49 773	CHF15 211	CHF7879	CHF35 799	CHF27 589
• ppFEV1 <40%:	CHF42 618	CHF91 794	CHF17 609	CHF8486	CHF80 482	CHF65 000

BSC: best supportive care; CAD: Canadian dollar; CHF: Swiss franc; CFTR: Cystic fibrosis transmembrane conductance regulator; CPI: consumer price indices; ppFEV1: percentage predicted forced expiratory volume in the first second; PPP: purchasing power parities.

* The annual inpatient and pharmacotherapy costs reported in the Canadian study (see Table 16) are aggregated. ** Costs for the following four categories presented in the ZIN report are aggregated: non-exacerbation-related costs (inpatient, outpatient, and pharmaceuticals) and exacerbation-related costs. *** In the CADTH and ZIN report, an analysis is performed in which costs for both the intervention and comparator group only differ according to the ppFEV1 category. **** In these HTA reports, the manufacturer assumed lower costs for patients receiving CFTR modulators. The cost for the comparator group (BSC – best supportive care) remains the same. For details of all underlying data and calculations, we refer to the original HTA reports.[4, 24, 62]

§ The year of costing was not reported. The report was published in 2022 and we assume the costs were taken from the previous year. # Source: Purchasing Power Parities for GDP (https://stats.oecd.org). & Source: Consumer price indices (all items) (https://stats.oecd.org).

8.8.3.3 Costs related to lung transplantation

For patients undergoing a lung transplant (see part 8.8.1.4), costs for Trikafta® and per ppFEV1 category are eliminated and costs linked to lung transplant intervention and follow-up are included. For lung transplantation costs, costs published in the identified literature are considered.

In the economic literature review (part 7.2.2.4) it was noticed that lung transplant and follow-up costs were not reported in the CADTH and INESSS report. The HAS study mentioned follow-up costs per year. However, lung transplantation costs were not reported separately. Hence, this study was not considered further. The US study was also not considered further because of the non-comparability of the costs for the European context.

The ZIN analysis did report costs transparently: €113 533 for a lung transplant and €12 030 for annual follow-up costs (Table 31).

A non-systematic literature search identified the publication of Whiting et al.[97] This study applied costs as reported for bilateral transplantation as these were considered to be the most common in CF patients (in 2010, 26 out of 29 transplants).[97] Costs were presented separately for the procedure and follow-up, with higher costs during the first years after the lung transplantation (Table 31).

The information from Whiting et al.[97] is included in the base case and the information from the ZIN report is modelled in a scenario analysis. These costs are converted via the PPP and CPI to CHF costs for the year 2022. The adjusted costs result in a relatively lower procedure cost based on Whiting's study compared to the ZIN analysis. On the other hand, annual costs are relatively higher in the latter study during the first three years after the procedure (Table 31).

Given the lack of information about the uncertainty around the costs, Whiting et al.[97] applied a random normal distribution with a standard error of 10%. Similar to the costs related to ppFEV1, a uniform distribution with a minimum and a maximum of +/- 20% is applied to these costs in our model.

Finally, Swiss-specific costs for lung transplant were received by the FOPH: ‘DRG A05B: Herz- oder Lungentransplantation oder Trennung von Siamesischen Zwillingen, Alter > 17 Jahre’, with an average cost of CHF115 280. This was included as a fixed cost in a separate scenario. Since there were no Swiss-specific follow-up costs available, this Swiss-specific cost for lung transplant was combined with the yearly follow-up costs from the Whiting et al.[97] study.

Table 31: Lung transplantation costs (unadjusted and adjusted to CHF, 2022)

	Whiting	ZIN	CH
Procedure LTx	£42 018	€113 533	CHF115 280
Yearly follow-up cost:		€12 030	
• 1st year:	£21 634		
• 2nd year:	£13 063		
• 3rd year:	£13 733		
• year 4-10:	£8249		
• subsequent years:	£4590		
Currency and year of costing	£, 2011	€, 2015	CHF, 2022
Adjustment:	Multiplication factor:	Multiplication factor:	/
• to CHF via PPP:#	x 1.9793	x 1.5257	
• to 2022 via CPI:&	x 1.0198	x 1.0412	
• combined:	x 2.0185	x 1.5886	
Adjusted costs:			
Procedure LTx	CHF84 815	CHF180 356	CHF115 280
Yearly follow-up cost:		CHF19 111	
• 1st year:	CHF43 669		
• 2nd year:	CHF26 368		
• 3rd year:	CHF27 720		
• year 4-10:	CHF16 651		
• subsequent years:	CHF9265		

CHF: Swiss franc; CPI: consumer price indices; LTx: lung transplantation; PPP: purchasing power parities.

Source: Purchasing Power Parities for GDP (https://stats.oecd.org). & Source: Consumer price indices (all items) (https://stats.oecd.org).

8.9 Uncertainty analysis

8.9.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was performed to account for parameter uncertainty in the model. The uncertainty in individual parameters was taken into account by applying probability distributions around individual parameters from which a number was randomly drawn in each simulation. These Monte Carlo simulations were repeated 1000 times to assess the influence of random variation in the parameter values on the outcomes. A probability distribution is constructed for the following variables:

- The ppFEV1 value at the age of 9 years: normal distribution with minimum and maximum limits
- The reduction in ppFEV1: beta distribution with an absolute standard deviation of 0.2%
- % lung transplantation: beta distribution
- Disease management costs: uniform distribution (+/- 20%)
- Lung transplantation costs (intervention and follow-up): uniform distribution (+/- 20%)
- Utilities: beta distribution (with reduced SD and correlation to avoid illogical values)

8.9.2 Deterministic sensitivity analyses

In addition to performing probabilistic sensitivity analysis, scenario analyses are also performed to calculate the impact of other uncertainties and assumptions on the results.

We note that when performing scenario analyses, the 'random' draws from the probability distributions for each parameter (see part 8.9.1) are remembered by the ModelRisk® software. Thus, the change in the result is entirely attributable to varying that particular parameter. Scenario analyses are performed for the following parameters:

- The survival curve of the comparator group (the HAS or ZIN figure)
- The impact on mortality (through the hazard ratio)
- The discount rate (0%, 3%, 5%, or 1.5% for effects and 4% for costs)
- The QoL values per ppFEV1 category: Acaster et al.[105] versus Tappenden et al.[107] data.
- The reduction in ppFEV1 in the comparator group: HAS/ZIN or ICER/Whiting data.
- The reduction in ppFEV1 in the intervention group: ZIN, HAS or ICER data
- % lung transplantation: Swiss data or information from CADTH or ICER report.
- Price discount Trikafta® (0% - 90%, in steps of 10%)
- Disease management costs: HAS, CADTH (equal/unequal assumption) or ZIN (equal/unequal assumption)
- Lung transplantation costs: Whiting and ZIN data (for both the intervention and follow-up) and Swiss costs (for the intervention).

8.10 Budget impact analysis

8.10.1 Objective

The objective of the budget-impact analysis (BIA) is to determine the potential budget impact of reimbursing Trikafta® (Elexacaftor, Tezacaftor, Ivacaftor) compared to no reimbursement.

8.10.2 Patient population

The population consists of patients aged 6 and older with CF who have at least one F508del mutation in the CFTR gene. First, the focus is on the budget impact of reimbursing Trikafta® in patients aged 6 to 11 years. Second, the budget impact of using Trikafta® in patients aged 12 years and older is added. The budget impact is presented for different genotypes depending on the availability of Swiss-specific epidemiological data.

8.10.3 Technology

The BIA reflects the addition of Trikafta® on top of best supportive care. The BIA will provide results separately for the impact of Trikafta®, Trikafta® follow-up costs, and disease management costs. Furthermore, a separate BIA will take into account the substitution of existing CFTR modulators Kalydeco®, Orkambi® and Symdeko® to the extent that these are already used in Switzerland in the target population.

8.10.4 Time horizon

The time horizon of the BIA is 5 years. No discount rate is applied in the BIA.

8.10.5 Perspective

The analysis is performed from a healthcare payers' perspective. Costs of healthcare services covered by the Swiss mandatory health insurance are analysed, irrespective of the actual payer (mandatory health insurer, other social insurer, government (federal government, cantons, communities) out-of-pocket). The analysis does not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs.

8.10.6 Model description

We used the results from the CUA analysis to estimate the total potential budget impact for patients aged 6-11 years. We refer to part 8.7.1 for the model structure. The budget impact includes the extra healthcare costs linked to the use of Trikafta® (treatment and follow-up costs) minus any offsets in these costs (disease management costs).

In the CUA, results were presented separately for the HAS and ZIN scenario, depending on which survival curve for the comparator group was taken into account. This distinction is not made for the BIA given the survival is >99% between 6 and 11 years in both models, resulting in similar results.

For patients aged 12 years and older, only the Trikafta® costs and substitution costs are taken into account. The economic model only reflects the impact for patients starting treatment at the age of 6 years. To use it for patients starting treatment at another age, evidence for these patients should first be assessed possibly leading to adjustments of the model about the impact on e.g. disease management costs and lung transplantations.

Swiss-specific data are used to include the decrease in budget impact related to the substitution of existing CFTR modulators.

8.10.7 Input data

The **data for estimating costs** for the intervention and comparator group are based on the economic model for patients aged 6-11 years. The costs for different categories are collected from the model. The categories that are relevant are the following: Trikafta® costs, Trikafta®-related follow-up costs, and disease management costs. Costs linked to lung transplantation are not relevant as they do not appear in the model in a population aged 6-11 years with CF. The European Cystic Fibrosis Society Patient Registry (ECFSPR) Annual Data Report (2021)[122] shows that the number of European CF patients alive in 2021 with transplanted lungs between the age of 6 and 11 years old is 0.2% (6/2869 patients). Excluding lung transplantation for the 5-year BIA seems thus to be justified. For all inputs of the BIA related to the cost of Trikafta®, follow-up costs, and evolution in ppFEV1 which is linked to the disease management costs, we refer to part 8.8.

The costs for the Trikafta® treatment and other CFTR modulators are based on the public price.

Epidemiological data is retrieved from the ECFSPR Annual Data Report (2021).[122] For Switzerland, the data reported reflect the national registry since all centres participate in the ECFSPR. The estimated coverage is >99%. Of the 1047 people with CF registered, 1036 are seen by the centres. Of these 1036 patients, genotyping is done in 1032 (99.6%). The data in the report show that the prevalence of the F508del variant varies considerably between the countries in Europe. In Switzerland, about 45% of patients are F508del homozygote (people who have two F508del variants), about 40% are F508del heterozygote (people who have one F508del variant and another known variant, that is not F508del) and the remaining 15% are people with CF who do not have a F508del variant. It is mentioned in the report that this might have a major impact on CFTR modulator eligibility.[122] Therefore, results will be presented separately for homozygous and heterozygous patients.

The report also presents the following information according to age, including the age category 6-11 years, 12-17 years and ≥18 years: people with CF in Switzerland and eligibility for at least one modulator (seen in 2021 who have never had a transplant). This information is presented in Table 32. We assume that the size of this population remains constant over the 5 years for which we conduct the BIA because of a similar inflow/outflow of patients in the different age categories. For the younger patients, this seems justified given the close to 100% survival for these patients (see KM curves in Figure 11 and Figure 12). However, for older patients, the estimated budget impact

could be an underestimation since the size of the population could increase over the years if Trikafta® treatment improves survival and is taken chronically. Also if lung transplantations would be avoided, the volume of patients taking Trikafta® would increase.

Table 32: People with CF and eligibility for at least one modulator (age 6-11 years and ≥12 years)

6-11 years	F508del homozygote	F508del heterozygote	Not F508del	Genotyping not done
Total	69	70	27	0
• eligible:	69	2	0	/
• not eligible:	0	68	27	0
≥12 years				
Total	305	266	96	0
• eligible:*	57 + 248	63 + 203	1 + 4	/
• not eligible:*	0 + 0	0 + 0	12 + 79	0 + 0

CF: cystic fibrosis. Source: ECFSPR Annual Data Report (2021)[122]

* The original report presents the data separately for patients aged 12-17 years and ≥18 years. In the above table, the data are disaggregated, in which the first and second number reflect the data for these two age categories, respectively.

Further information is presented in the ECFSPR Annual Data Report for the patients eligible for at least one CFTR modulator. Table 33 gives an overview of the CFTR modulator therapies homozygote and heterozygote patients receive.

Table 33: CFTR modulator therapy for F508del homozygote and heterozygote people with CF eligible for at least one modulator (age 6-11 years and ≥12 years)

6-11 years	F508del homozygote	F508del heterozygote
Total	69	2
• no CFTR modulator:	34	0
• Ivacaftor (Kalydeco®):	0	2
• Lumacaftor/Ivacaftor (Orkambi®):	29	0
• Tezacaftor/Ivacaftor (Symdeko®):	4	0
• Elexacaftor/Tezacaftor/Ivacaftor (Trikafta®):	2	0
≥12 years		
Total	305	266
• no CFTR modulator:*	10 + 17	6 + 52
• Ivacaftor (Kalydeco®):*	0 + 0	4 + 9
• Lumacaftor/Ivacaftor (Orkambi®):*	0 + 4	0 + 0
• Tezacaftor/Ivacaftor (Symdeko®):*	0 + 5	2 + 1
• Elexacaftor/Tezacaftor/Ivacaftor (Trikafta®):*	47 + 222	51 + 141

CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator. Source: ECFSPR Annual Data Report (2021)[122]

* The original report presents the data separately for patients aged 12-17 years and ≥18 years. In the above table, the data are disaggregated, in which the first and second number reflect the data for these two age categories, respectively.

The cost for these CFTR modulator therapies is extracted from the Spezialitätenliste. Table 34 and Table 35 provide information on the recommended dosage, price per package and yearly cost. Since we have no information on potential negotiated price discounts, the list price is taken into account. The costs for Kalydeco®, Orkambi® and Symdeko® that would be replaced by Trikafta® are subtracted from the total budget impact.

Table 34: CFTR modulator treatments – recommended dosage

CFTR modulator	Morning dose	Evening dose
Ivacaftor (Kalydeco®)	1 tablet Kalydeco®	1 tablet Kalydeco®
Lumacaftor/Ivacaftor (Orkambi®)	2 tablets Orkambi®	2 tablets Orkambi®
Tezacaftor/Ivacaftor (Symdeko®)	1 tablet Symdeko®	1 tablet Kalydeco®

We refer to Table 27 for the recommended dosage of Trikafta®.

Table 35: CFTR modulator treatments – price information

Content	Public price (incl.VAT)	Price per day*	Price per year
Ivacaftor (Kalydeco®): • 56 tablets (Ivacaftorum 150 mg)	CHF13 561.85	CHF484.35	CHF176 788
Lumacaftor/Ivacaftor (Orkambi®): • 112 tablets (age 6-11 years:** Lumacaftorum 100 mg, Ivacaftorum 125 mg) (age ≥12 years:** Lumacaftorum 200 mg, Ivacaftorum 125 mg)	CHF10 643.55	CHF380.13	CHF138 746
Tezacaftor/Ivacaftor (Symdeko®): • 56 tablets (Tezacaftorum 100 mg, Ivacaftorum 150 mg + Ivacaftorum 150 mg)	CHF11 850.30	CHF423.23	CHF154 477

VAT: value added tax. Source: “Spezialitätenliste” (www.spezialitaetenliste.ch). * see recommended dosage in Table 34. We refer to Table 28 for the price information related to Trikafta®. ** The public price is the same for both packages with the 100 mg or 200 mg lumacaftor tablets.

8.10.8 Base case and scenario analyses

The budget impact is calculated separately for the 69 homozygote and 70 heterozygote patients aged 6-11 years and the 305 homozygote and 266 heterozygote patients aged ≥12 years. At the first level, only the cost of Trikafta® is taken into account. In the INESSS report,[63] experts indicated that as soon as the treatment would be available, uptake would be very fast, reaching almost 100% within three months. Therefore, a 100% market penetration is assumed from the start of the BIA.

At a second level, for patients aged 6-11 years, other costs included in the model are taken into account (Trikafta® follow-up costs and disease management costs). A scenario with equal disease management costs per ppFEV1 category is modelled ('HAS' scenario in Table 30), as well as a scenario with lower costs per ppFEV1 category for patients receiving Trikafta® ('CADTH lower CFTR' in Table 30). There are arguments in favour of both scenarios: e.g. the use of Trikafta® might reduce disease management costs in favour of using lower costs in the intervention group. However, if this lower cost is only reflected if patients in the comparator group end up in a worse ppFEV1 category, equal costs per ppFEV1 category could be chosen. No value judgement is made to prefer one scenario above the other. Therefore, we don’t select one of these scenarios as the

base case. Instead, we refer to these two scenarios in the results in a neutral way as ‘equal’ and ‘unequal’ disease management costs.

At a third level, for both patients aged 6-11 years and ≥12 years, the cost of the other CFTR modulators Kalydeco®, Orkambi® and Symdeko® are subtracted by applying the information from Table 33 and assuming 100% compliance for simplicity (similar to the 99.4% compliance assumed for Trikafta®).

Calculations for the BIA are based on the model with the HAS survival curve in the comparator group and a mortality hazard ratio of 0.1. As mentioned before, survival in the intervention and comparator group is >99% between 6 and 11 years of age. Modelling the HAS or ZIN survival curve for the comparator arm (see part 8.8.1.1) or adjusting the hazard ratio does not influence results. Therefore, other scenarios are not modelled separately.

Many different scenarios can be performed for the budget impact, changing e.g. the target population, time horizon, market penetration, compliance, price discount, etc. The results are presented in a transparent table, allowing manual adjustments for changes in these variables.

8.10.9 Model software and validation of the model

See part 8.7.2.

9. Results economic evaluation and budget impact analysis for Switzerland

9.1 Economic evaluation

9.1.1 Base case results

Due to the lack of hard evidence about the impact of the intervention on both survival and quality of life, many assumptions were made. The results should therefore be interpreted with caution.

Given that there is no real hard evidence to prefer one scenario over the other, the results are presented side by side without any value judgment as to which scenario is more likely than another. The modelled scenarios show the possible impact of the different assumptions on the intervention's cost-effectiveness and the most determining variables.

Impact on (un)discounted life-years gained

Table 36 presents the impact on life expectancy by applying the different hazard ratios. This is the life expectancy for patients aged 6 years, where the outcomes were not discounted and where the half-cycle correction was taken into account. Applying different mortality hazard ratios has a large impact on the life years gained (LYG). With a hazard ratio of 0.9 or 0.8, the LYG are smaller than 3 years. With a hazard ratio of 0.1, they are about 26 years in the HAS scenario and almost 34 years in the ZIN scenario.

The life years gained are larger when the survival curve for the comparator group from the ZIN report is used. This is caused by the faster decline in survival in the comparator group in the ZIN curve compared to the survival curve for the comparator group in the HAS report: for example, on the KM curve from the ZIN report (see Figure 11 in part 8.8.1.1), about 80% of patients are still alive at the age of 30 years, while this is about 90% in the HAS figure (see Figure 12 in part 8.8.1.1). Applying the same mortality hazard ratio to a population with a worse survival leads to a larger absolute treatment effect expressed in life years gained.

Table 36: Life expectancy (years) at the age of 6 years and life-years gained (undiscounted and inclusive half-cycle correction)

Hazard ratio	1	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	Swiss population
	HAS survival curve										
Life expectancy	42.1	43.2	44.5	45.9	47.5	49.5	51.9	55.0	59.7	67.9	77.1
LYG	/	1.1	2.3	3.8	5.4	7.3	9.7	12.9	17.6	25.8	
	ZIN survival curve										
Life expectancy	34.8	36.1	37.7	39.5	41.7	44.4	47.8	52.5	59.1	68.5	77.1
LYG	/	1.3	2.9	4.7	6.9	9.6	13.0	17.7	24.3	33.7	

LYG: life-years gained.

In Table 37, we show the same results, but this time with the impact of discounting. The impact is very large. Without applying a discount rate, a hazard ratio of 0.1 leads to about 26 and 34 LYG, in the HAS and ZIN scenario, respectively. With a discount rate of 3%, this is only 5.4 and 7.6 LYG, respectively. This is because the life years gained for children aged 6 occur relatively far into the future (see Figure 14 and Figure 15).

Table 37: Life expectancy (years) at the age of 6 years and life-years gained (discounted and inclusive half-cycle correction)

Hazard ratio	1	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1
	HAS survival curve									
Life expectancy	22.9	23.3	23.6	24.0	24.4	24.9	25.5	26.2	27.0	28.3
LYG	/	0.3	0.7	1.1	1.5	2.0	2.5	3.2	4.1	5.4
	ZIN survival curve									
Life expectancy	20.4	20.9	21.3	21.9	22.5	23.2	24.0	25.1	26.4	28.1
LYG	/	0.4	0.9	1.4	2.1	2.8	3.6	4.6	5.9	7.6

LYG: life-years gained.

Figure 14: Survival curve for the comparator group (HAS scenario) and intervention group (hazard ratio 0.1)

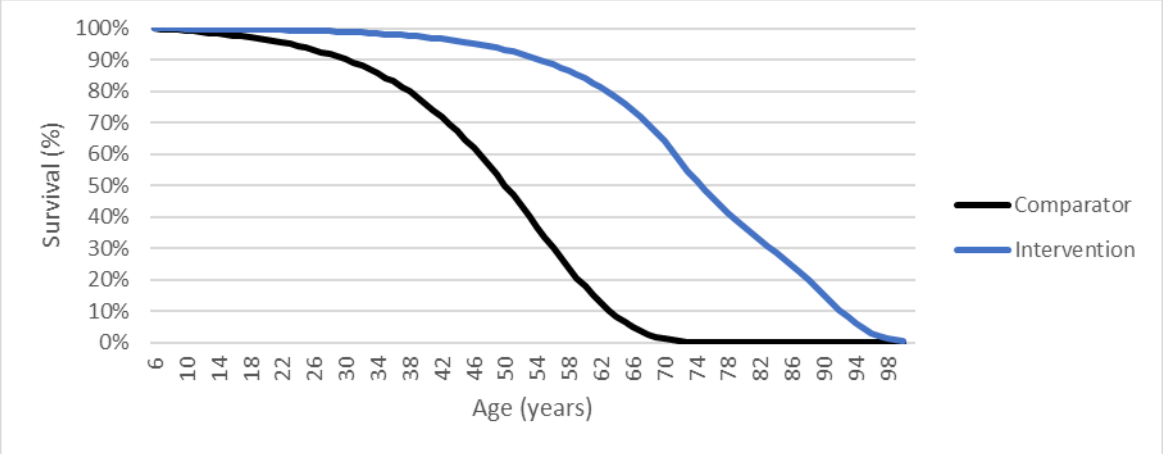
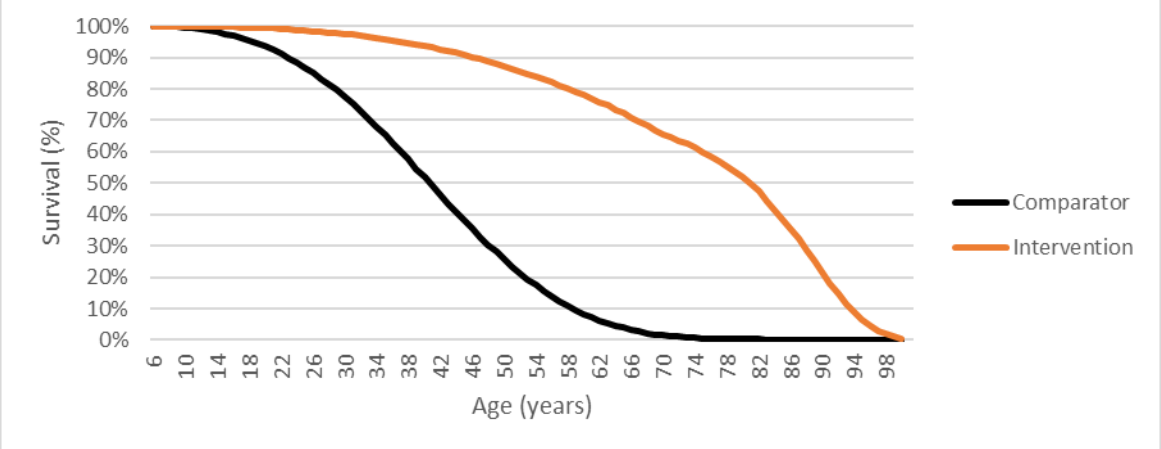


Figure 15: Survival curve for the comparator group (ZIN scenario) and intervention group (hazard ratio 0.1)



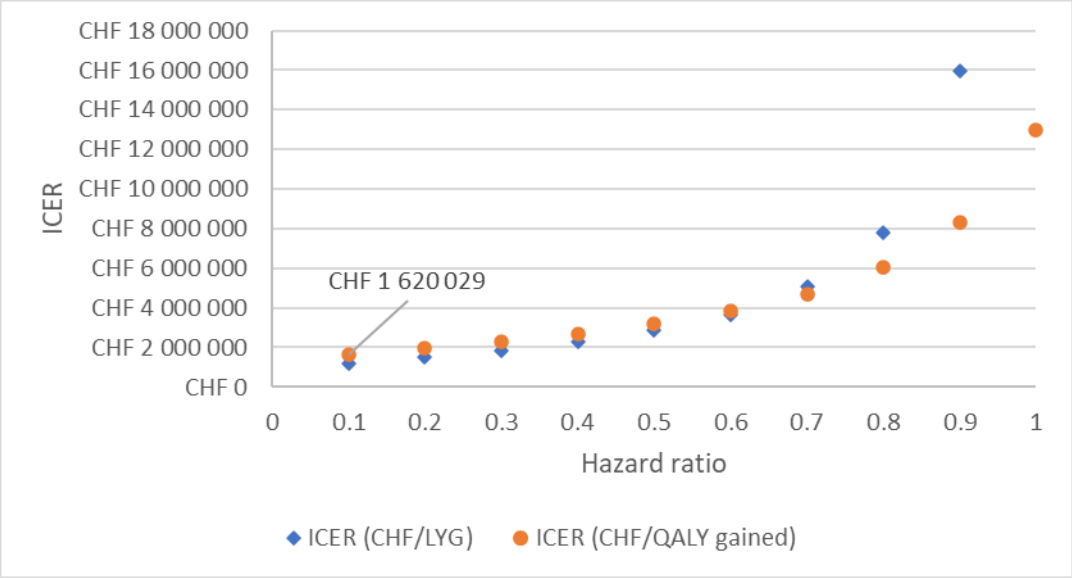
Remark: In what follows, we present the results with the survival curve for the comparator group from both the HAS and ZIN reports. This is indicated by adding (HAS) or (ZIN) in the text or titles of the tables and figures.

9.1.2 Probabilistic sensitivity analysis

9.1.2.1 Impact hazard ratio

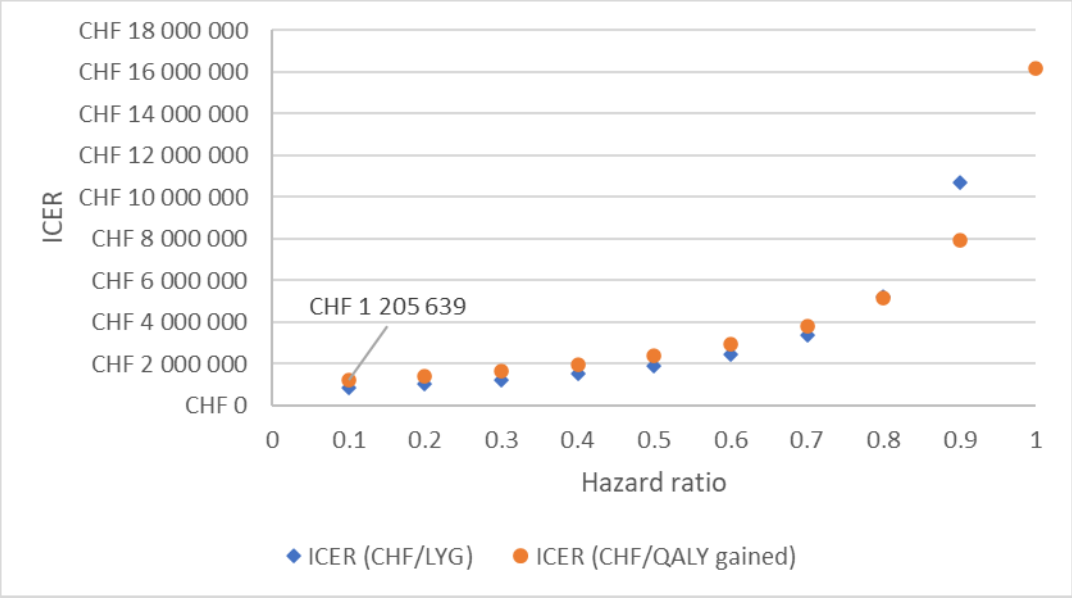
Figure 16, Figure 17, Table 38 and Table 39 show the results of different hazard ratios on either incremental costs (IC), incremental effects (IE) expressed in LYG and quality-adjusted life years (QALYs) gained and incremental cost-effectiveness ratios (ICERs) expressed in CHF/LYG and CHF/QALY gained. With a hazard ratio of 0.1, we obtain ICERs of about CHF1.6 million (HAS) and CHF1.2 million (ZIN) per QALY gained.

Figure 16: ICERs – impact of the hazard ratio (HAS)



ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALYs: quality-adjusted life years.

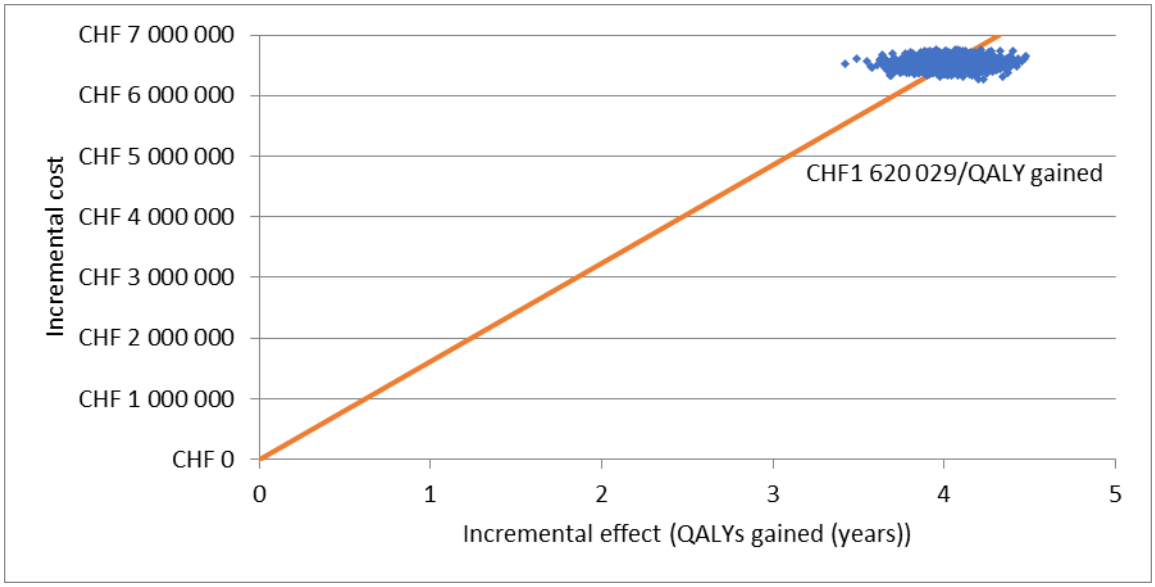
Figure 17: ICERs – impact of the hazard ratio (ZIN)

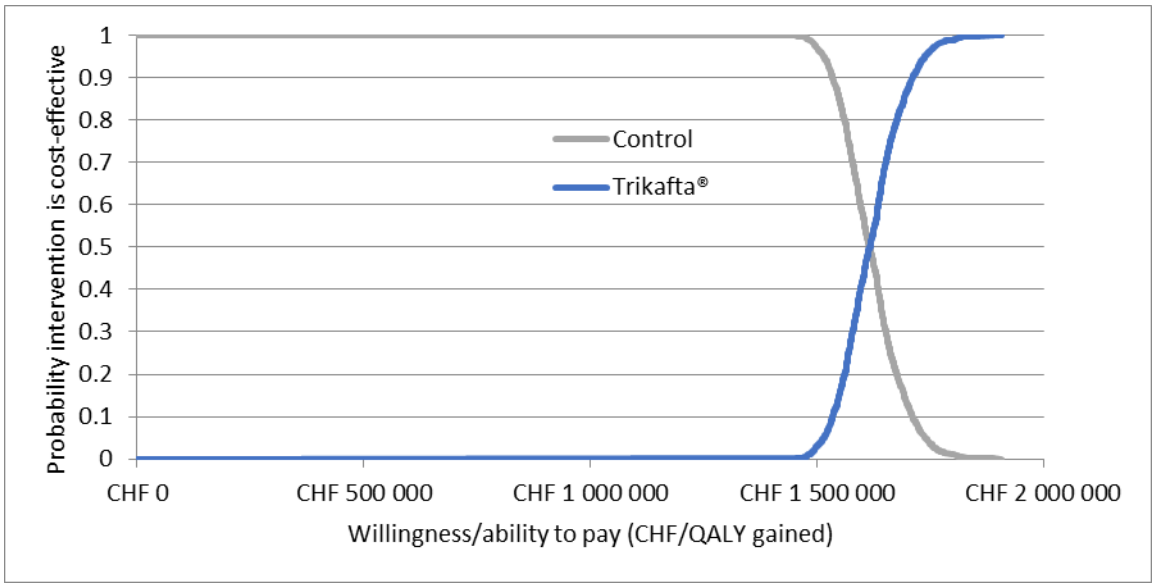


ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALYs: quality-adjusted life years.

The results of the scenario applying a hazard ratio of 0.1 are presented on the cost-effectiveness plane and the cost-effectiveness acceptability curve for both the HAS (Figure 18) and ZIN scenarios (Figure 19).

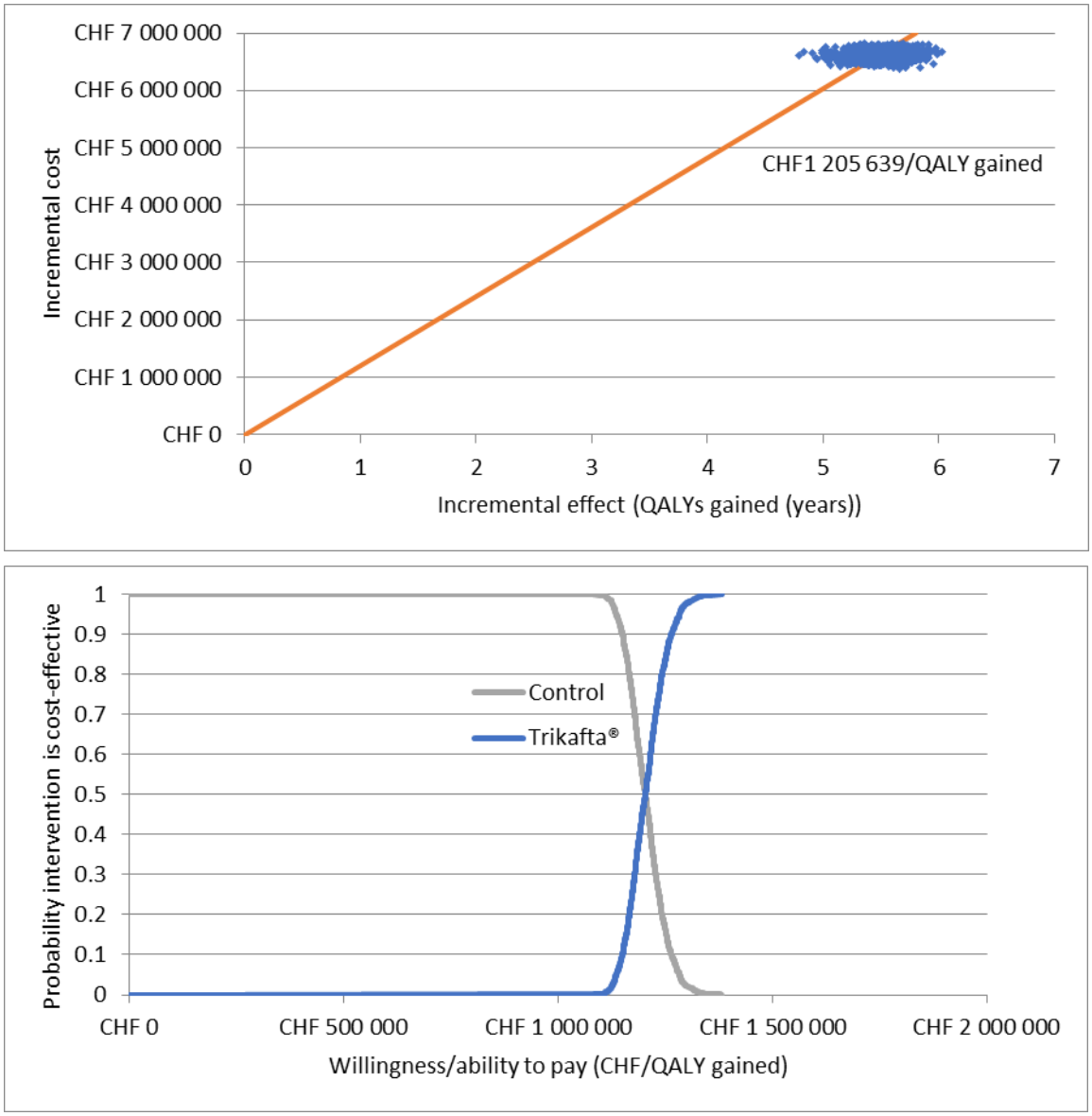
Figure 18: Cost-effectiveness plane and cost-effectiveness acceptability curve (HAS)





QALYs: quality-adjusted life years. Remark: the above figure presents the results of the scenario applying a mortality hazard ratio of 0.1.

Figure 19: Cost-effectiveness plane and cost-effectiveness acceptability curve (ZIN)



QALYs: quality-adjusted life years. Remark: the above figure presents the results of the scenario applying a mortality hazard ratio of 0.1.

Table 38: IC, IE and ICERs – impact of the hazard ratio (HAS)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (CHF/LYG) ICER (CHF/QALY gained)
Hazard ratio	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
1	CHF 861 982 (751 897 - 979 228)	CHF 5 905 458 (5 812 869 - 5 998 525)	CHF 5 043 476 (4 897 765 - 5 183 554)	22.95	22.95	0.00	/
				16.17 (15.04 - 17.14)	16.58 (15.35 - 17.64)	0.41 (0.26 - 0.59)	CHF 12 967 534 (8 537 565 - 19 783 831)
0.9	CHF 861 982 (751 897 - 979 228)	CHF 5 993 619 (5 898 161 - 6 088 989)	CHF 5 131 637 (4 984 540 - 5 274 584)	22.95	23.27	0.32	CHF 15 940 913 (15 483 971 - 16 384 964)
				16.17 (15.04 - 17.14)	16.80 (15.55 - 17.88)	0.63 (0.47 - 0.82)	CHF 8 300 628 (6 247 721 - 11 038 331)
0.8	CHF 861 982 (751 897 - 979 228)	CHF 6 089 570 (5 991 247 - 6 186 929)	CHF 5 227 588 (5 079 112 - 5 372 532)	22.95	23.62	0.67	CHF 7 783 988 (7 562 903 - 7 999 813)
				16.17 (15.04 - 17.14)	17.04 (15.78 - 18.14)	0.87 (0.70 - 1.06)	CHF 6 056 298 (4 866 176 - 7 507 716)
0.7	CHF 861 982 (751 897 - 979 228)	CHF 6 195 053 (6 094 203 - 6 295 095)	CHF 5 333 071 (5 182 041 - 5 479 907)	22.95	24.00	1.06	CHF 5 054 363 (4 911 225 - 5 193 525)
				16.17 (15.04 - 17.14)	17.31 (16.03 - 18.42)	1.14 (0.95 - 1.34)	CHF 4 720 728 (3 959 399 - 5 633 299)
0.6	CHF 861 982 (751 897 - 979 228)	CHF 6 312 547 (6 208 693 - 6 415 009)	CHF 5 450 565 (5 297 383 - 5 599 538)	22.95	24.43	1.48	CHF 3 679 503 (3 576 095 - 3 780 071)
				16.17 (15.04 - 17.14)	17.60 (16.30 - 18.73)	1.43 (1.22 - 1.64)	CHF 3 827 299 (3 300 819 - 4 441 275)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (CHF/LYG) ICER (CHF/QALY gained)
	mean	**mean**	**mean**	**mean**	**mean**	**mean**	**mean**
Hazard ratio	**(2.5% - 97.5%)**	**(2.5% - 97.5%)**	**(2.5% - 97.5%)**	**(2.5% - 97.5%)**	**(2.5% - 97.5%)**	**(2.5% - 97.5%)**	**(2.5% - 97.5%)**
0.5	CHF 861 982	CHF 6 445 800	CHF 5 583 818	22.95	24.91	1.96	CHF 2 844 009
	(751 897 - 979 228)	(6 338 187 - 6 550 653)	(5 428 412 - 5 735 259)				(2 764 856 - 2 921 142)
				16.17	17.93	1.76	CHF 3 181 321
				(15.04 - 17.14)	(16.61 - 19.08)	(1.53 - 1.99)	(2 799 539 - 3 616 687)
0.4	CHF 861 982	CHF 6 600 982	CHF 5 739 000	22.95	25.47	2.52	CHF 2 274 678
	(751 897 - 979 228)	(6 489 369 - 6 710 446)	(5 579 537 - 5 893 678)				(2 211 474 - 2 335 985)
				16.17	18.31	2.14	CHF 2 685 606
				(15.04 - 17.14)	(16.97 - 19.48)	(1.89 - 2.39)	(2 398 966 - 3 016 376)
0.3	CHF 861 982	CHF 6 789 521	CHF 5 927 539	22.95	26.15	3.20	CHF 1 851 950
	(751 897 - 979 228)	(6 672 077 - 6 902 916)	(5 765 111 - 6 087 452)				(1 801 202 - 1 901 911)
				16.17	18.77	2.60	CHF 2 284 161
				(15.04 - 17.14)	(17.40 - 19.96)	(2.33 - 2.85)	(2 062 399 - 2 535 768)
0.2	CHF 861 982	CHF 7 036 180	CHF 6 174 198	22.95	27.03	4.08	CHF 1 511 490
	(751 897 - 979 228)	(6 912 330 - 7 157 230)	(6 007 544 - 6 339 905)				(1 470 692 - 1 552 057)
				16.17	19.36	3.19	CHF 1 938 750
				(15.04 - 17.14)	(17.96 - 20.59)	(2.89 - 3.46)	(1 769 961 - 2 129 577)
0.1	CHF 861 982	CHF 7 399 751	CHF 6 537 769	22.95	28.34	5.39	CHF 1 213 756
	(751 897 - 979 228)	(7 268 189 - 7 529 035)	(6 363 152 - 6 713 133)				(1 181 338 - 1 246 313)
				16.17	20.21	4.04	CHF 1 620 029
				(15.04 - 17.14)	(18.77 - 21.47)	(3.70 - 4.35)	(1 496 608 - 1 761 751)

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LY: life years; LYG: life-years gained; QALYs: quality-adjusted life years.

Table 39: IC, IE and ICERs – impact of the hazard ratio (ZIN)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (CHF/LYG) ICER (CHF/QALY gained)
Hazard ratio	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
1	CHF 710 727 (619 212 - 808 900)	CHF 5 220 541 (5 147 383 - 5 296 442)	CHF 4 509 814 (4 391 172 - 4 624 959)	20.43	20.43	0.00	/
				14.51 (13.48 - 15.41)	14.80 (13.71 - 15.76)	0.29 (0.20 - 0.41)	CHF 16 156 999 (11 039 568 - 23 142 499)
0.9	CHF 710 727 (619 212 - 808 900)	CHF 5 337 735 (5 261 271 - 5 416 368)	CHF 4 627 008 (4 506 457 - 4 744 635)	20.43	20.86	0.43	CHF 10 730 988 (10 451 405 - 11 003 788)
				14.51 (13.48 - 15.41)	15.10 (13.98 - 16.08)	0.59 (0.48 - 0.72)	CHF 7 905 528 (6 405 876 - 9 631 326)
0.8	CHF 710 727 (619 212 - 808 900)	CHF 5 468 122 (5 387 595 - 5 549 765)	CHF 4 757 395 (4 635 826 - 4 877 233)	20.43	21.34	0.91	CHF 5 229 034 (5 095 413 - 5 360 753)
				14.51 (13.48 - 15.41)	15.44 (14.29 - 16.44)	0.93 (0.79 - 1.06)	CHF 5 166 947 (4 429 290 - 5 980 297)
0.7	CHF 710 727 (619 212 - 808 900)	CHF 5 614 886 (5 531 071 - 5 700 162)	CHF 4 904 160 (4 778 943 - 5 027 036)	20.43	21.88	1.45	CHF 3 388 898 (3 302 370 - 3 473 809)
				14.51 (13.48 - 15.41)	15.81 (14.64 - 16.83)	1.30 (1.15 - 1.46)	CHF 3 786 696 (3 356 298 - 4 262 978)
0.6	CHF 710 727 (619 212 - 808 900)	CHF 5 782 471 (5 693 969 - 5 871 547)	CHF 5 071 744 (4 943 283 - 5 197 998)	20.43	22.49	2.06	CHF 2 463 317 (2 400 924 - 2 524 638)
				14.51 (13.48 - 15.41)	16.24 (15.04 - 17.28)	1.72 (1.54 - 1.89)	CHF 2 950 179 (2 662 028 - 3 271 967)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (CHF/LYG) ICER (CHF/QALY gained)
	mean	**mean**	**mean**	**mean**	**mean**	**mean**	**mean**
Hazard ratio	**(2.5% - 97.5%)**	**(2.5% - 97.5%)**	**(2.5% - 97.5%)**	**(2.5% - 97.5%)**	**(2.5% - 97.5%)**	**(2.5% - 97.5%)**	**(2.5% - 97.5%)**
0.5	CHF 710 727	CHF 5 977 293	CHF 5 266 566	20.43	23.20	2.77	CHF 1 902 720
	(619 212 - 808 900)	(5 883 038 - 6 070 423)	(5 132 714 - 5 394 428)				(1 854 361 - 1 948 914)
				14.51	16.73	2.21	CHF 2 385 500
				(13.48 - 15.41)	(15.49 - 17.80)	(2.00 - 2.41)	(2 177 800 - 2 618 336)
0.4	CHF 710 727	CHF 6 209 041	CHF 5 498 314	20.43	24.04	3.61	CHF 1 523 689
	(619 212 - 808 900)	(6 108 598 - 6 307 149)	(5 360 974 - 5 632 693)				(1 485 629 - 1 560 928)
				14.51	17.30	2.79	CHF 1 975 594
				(13.48 - 15.41)	(16.03 - 18.40)	(2.54 - 3.01)	(1 817 295 - 2 151 220)
0.3	CHF 710 727	CHF 6 493 297	CHF 5 782 570	20.43	25.06	4.64	CHF 1 247 214
	(619 212 - 808 900)	(6 385 292 - 6 597 491)	(5 640 082 - 5 924 527)				(1 216 482 - 1 277 833)
				14.51	18.00	3.49	CHF 1 661 368
				(13.48 - 15.41)	(16.69 - 19.14)	(3.20 - 3.74)	(1 540 412 - 1 800 257)
0.2	CHF 710 727	CHF 6 856 526	CHF 6 145 799	20.43	26.37	5.95	CHF 1 033 523
	(619 212 - 808 900)	(6 739 558 - 6 971 715)	(5 993 667 - 6 296 647)				(1 007 939 - 1 058 890)
				14.51	18.88	4.37	CHF 1 409 625
				(13.48 - 15.41)	(17.53 - 20.07)	(4.03 - 4.67)	(1 314 676 - 1 523 169)
0.1	CHF 710 727	CHF 7 329 176	CHF 6 618 450	20.43	28.08	7.65	CHF 865 450
	(619 212 - 808 900)	(7 202 041 - 7 457 212)	(6 452 513 - 6 778 058)				(843 752 - 886 321)
				14.51	20.01	5.50	CHF 1 205 639
				(13.48 - 15.41)	(18.59 - 21.24)	(5.10 - 5.85)	(1 127 235 - 1 296 594)

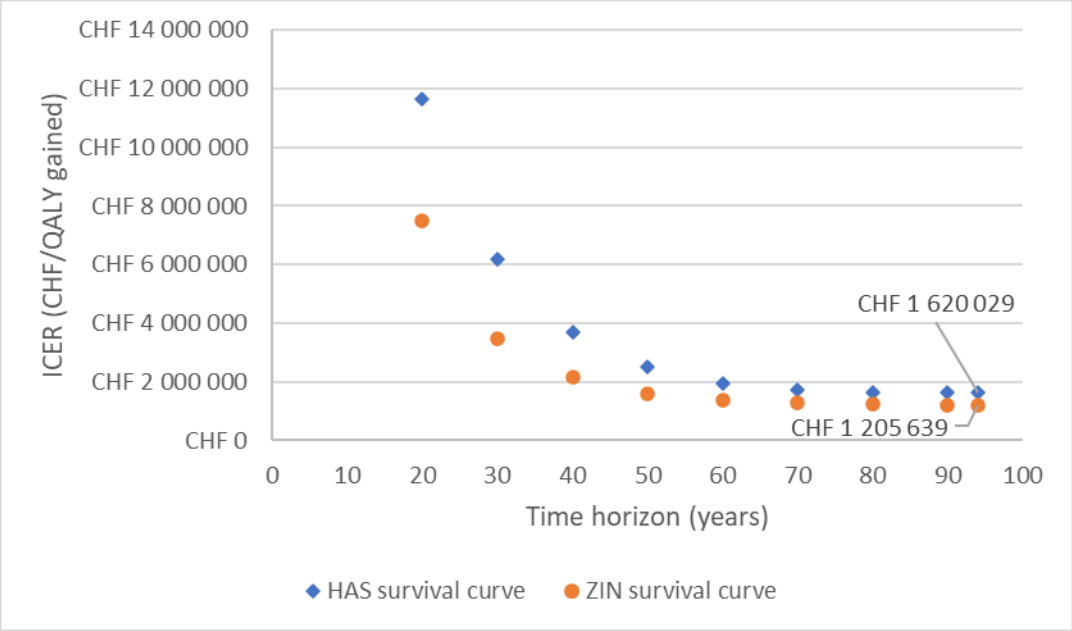
IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LY: life years; LYG: life-years gained; QALYs: quality-adjusted life years.

Remark: In what follows, it is impossible to present the results for all hazard ratios further. For practical reasons, we chose to apply all other scenario analyses to the scenario where a hazard ratio of 0.1 was applied. If evidence showed that the impact on mortality would be lower (and all other assumptions considered equal), the ICERs would be higher, and vice versa.

9.1.2.2 Impact time horizon

Figure 20, Table 40 and Table 41 show that applying a shorter or longer time horizon also has a significant impact on the ICERs. Costs for Trikafta® are already incurred in the short term and are recurrent annually. In contrast, the effects in life years gained are in the future. With a time horizon below 40 years, ICERs are above CHF2 million per QALY gained.

Figure 20: ICERs – impact of the time horizon (HAS & ZIN)



ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

For the results with a 10-year time horizon, please refer to the following tables.

Table 40: ICERs – impact of the time horizon (HAS)

	ICER (CHF/LYG)	ICER (CHF/QALY gained)
Time horizon	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
10 years	CHF 29 381 581 (28 825 599 - 29 975 541)	CHF 31 488 939 (28 157 670 - 34 226 418)
20 years	CHF 11 464 519 (11 247 389 - 11 679 513)	CHF 11 636 043 (10 323 751 - 12 670 004)
30 years	CHF 5 811 255 (5 670 215 - 5 947 416)	CHF 6 160 500 (5 477 180 - 6 726 142)
40 years	CHF 3 300 096 (3 210 788 - 3 387 680)	CHF 3 701 012 (3 282 491 - 4 124 715)
50 years	CHF 2 088 007 (2 029 814 - 2 143 255)	CHF 2 492 517 (2 238 694 - 2 783 662)
60 years	CHF 1 527 723 (1 485 956 - 1 569 100)	CHF 1 934 867 (1 758 172 - 2 133 974)
70 years	CHF 1 308 381 (1 273 250 - 1 343 694)	CHF 1 713 839 (1 575 151 - 1 874 312)
80 years	CHF 1 234 026 (1 201 393 - 1 267 144)	CHF 1 639 906 (1 512 723 - 1 785 617)
90 years	CHF 1 214 465 (1 182 051 - 1 247 043)	CHF 1 620 732 (1 497 194 - 1 762 683)
Lifetime (94 years)	CHF 1 213 756 (1 181 338 - 1 246 313)	CHF 1 620 029 (1 496 608 - 1 761 751)

ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALYs: quality-adjusted life years.

Table 41: ICERs – impact of the time horizon (ZIN)

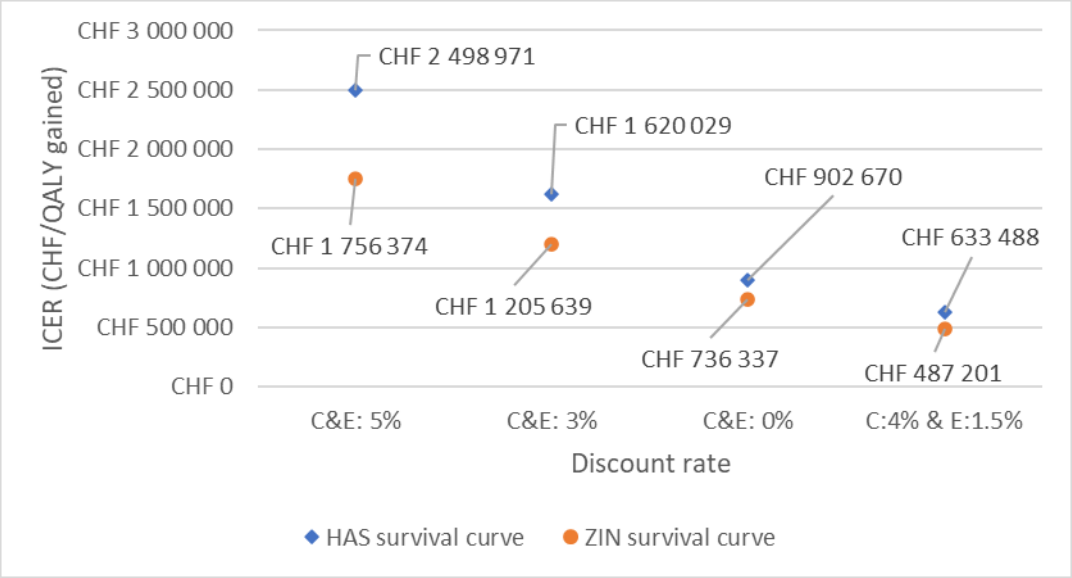
	ICER (CHF/LYG)	ICER (CHF/QALY gained)
Time horizon	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
10 years	CHF 27 399 660 (26 881 378 - 27 953 439)	CHF 29 823 610 (26 780 288 - 32 376 969)
20 years	CHF 6 511 256 (6 390 095 - 6 631 380)	CHF 7 511 044 (6 834 949 - 8 133 630)
30 years	CHF 2 831 190 (2 766 746 - 2 894 299)	CHF 3 472 787 (3 182 358 - 3 759 998)
40 years	CHF 1 682 265 (1 640 776 - 1 722 958)	CHF 2 146 139 (1 976 616 - 2 334 101)
50 years	CHF 1 223 785 (1 193 080 - 1 254 042)	CHF 1 608 360 (1 486 001 - 1 746 241)
60 years	CHF 1 019 692 (994 218 - 1 044 784)	CHF 1 374 063 (1 275 690 - 1 487 443)
70 years	CHF 923 573 (900 355 - 946 123)	CHF 1 267 363 (1 182 161 - 1 368 922)
80 years	CHF 878 449 (856 517 - 899 654)	CHF 1 219 237 (1 139 192 - 1 311 905)
90 years	CHF 865 911 (844 218 - 886 796)	CHF 1 206 128 (1 127 642 - 1 297 136)
Lifetime (94 years)	CHF 865 450 (843 752 - 886 321)	CHF 1 205 639 (1 127 235 - 1 296 594)

ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALYs: quality-adjusted life years.

9.1.2.3 Impact discount rate

In line with the impact of the time horizon, Figure 21, Table 42 and Table 43 show the major impact of the discount rate. A lower discount rate lowers the ICER and vice versa. A differential discount rate, as applied in the Netherlands, has an even greater impact on the ICERs. In this scenario, the higher discounting of future costs (discount rate 4%) causes the incremental costs to be lowered more strongly compared to the incremental effects (discount rate 1.5%). It is important to consider this difference in discount rate when comparing results from other studies.

Figure 21: ICERs – impact of the discount rate (HAS & ZIN)



C: costs; E: effects; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 42: IC, IE and ICERs – impact of the discount rate (HAS)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (CHF/LYG) ICER (CHF/QALY gained)
	mean	mean	mean	mean	mean	mean	mean
Discount rate	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)
C&E: 3%	CHF 861 982	CHF 7 399 751	CHF 6 537 769	22.95	28.34	5.39	CHF 1 213 756
	(751 897 - 979 228)	(7 268 189 - 7 529 035)	(6 363 152 - 6 713 133)				(1 181 338 - 1 246 313)
				16.17	20.21	4.04	CHF 1 620 029
				(15.04 - 17.14)	(18.77 - 21.47)	(3.70 - 4.35)	(1 496 608 - 1 761 751)
C&E: 0%	CHF 1 900 065	CHF 18 255 874	CHF 16 355 809	42.14	67.92	25.79	CHF 634 302
	(1 650 402 - 2 178 277)	(17 819 496 - 18 681 181)	(15 813 190 - 16 863 037)				(613 258 - 653 973)
				29.02	47.16	18.14	CHF 902 670
				(27.07 - 30.73)	(43.93 - 50.04)	(16.85 - 19.34)	(840 910 - 973 712)
C&E: 5%	CHF 561 835	CHF 4 881 560	CHF 4 319 725	16.79	18.99	2.20	CHF 1 960 442
	(489 835 - 637 239)	(4 809 733 - 4 953 245)	(4 216 872 - 4 421 823)				(1 913 764 - 2 006 778)
				11.96	13.69	1.73	CHF 2 498 971
				(11.11 - 12.70)	(12.69 - 14.56)	(1.57 - 1.88)	(2 295 181 - 2 729 349)
C: 4%	CHF 689 614	CHF 5 921 888	CHF 5 232 274	30.37	41.77	11.40	CHF 459 113
E: 1.5%	(602 422 - 783 035)	(5 825 604 - 6 016 052)	(5 099 909 - 5 363 191)				(447 499 - 470 601)
				21.18	29.45	8.27	CHF 633 488
				(19.73 - 22.44)	(27.38 - 31.23)	(7.63 - 8.85)	(589 611 - 685 469)

C: costs; E: effects; IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LY: life years; LYG: life-years gained; QALYs: quality-adjusted life years.

Table 43: IC, IE and ICERs – impact of the discount rate (ZIN)

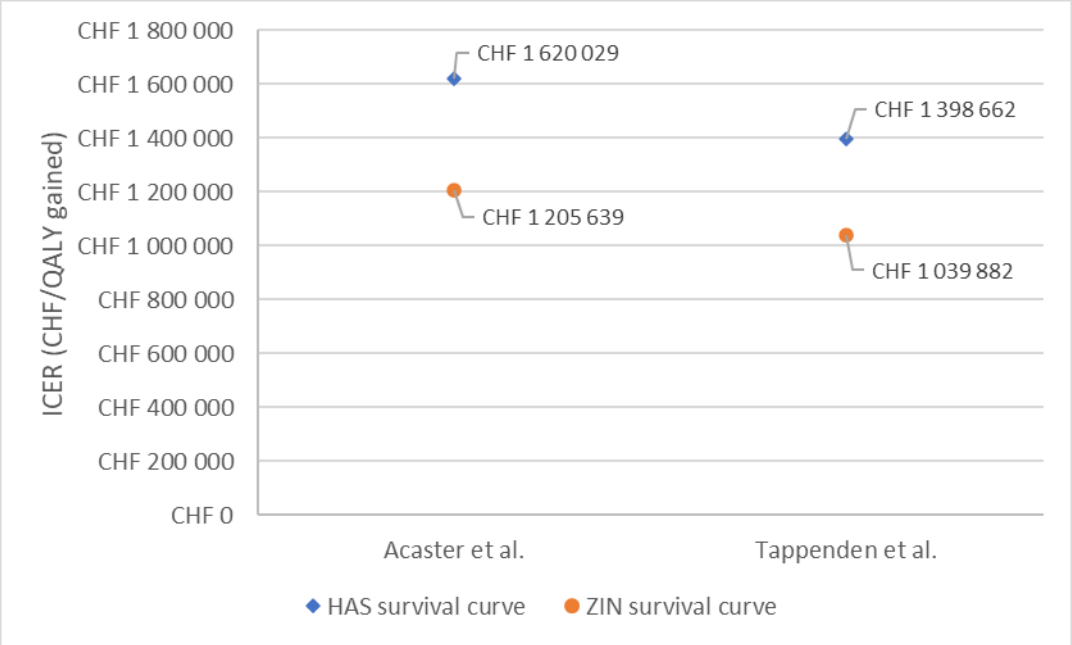
	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (CHF/LYG) ICER (CHF/QALY gained)
	mean	mean	mean	mean	mean	mean	mean
Discount rate	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)
C&E: 3%	CHF 710 727	CHF 7 329 176	CHF 6 618 450	20.43	28.08	7.65	CHF 865 450
	(619 212 - 808 900)	(7 202 041 - 7 457 212)	(6 452 513 - 6 778 058)				(843 752 - 886 321)
				14.51	20.01	5.50	CHF 1 205 639
				(13.48 - 15.41)	(18.59 - 21.24)	(5.10 - 5.85)	(1 127 235 - 1 296 594)
C&E: 0%	CHF 1 436 880	CHF 18 421 766	CHF 16 984 886	34.81	68.52	33.71	CHF 503 867
	(1 253 740 - 1 639 065)	(17 975 850 - 18 844 934)	(16 471 868 - 17 480 628)				(488 648 - 518 573)
				24.29	47.38	23.09	CHF 736 337
				(22.62 - 25.74)	(44.23 - 50.26)	(21.54 - 24.53)	(688 088 - 789 641)
C&E: 5%	CHF 485 350	CHF 4 832 254	CHF 4 346 904	15.47	18.81	3.34	CHF 1 299 848
	(423 098 - 551 126)	(4 761 674 - 4 902 592)	(4 250 354 - 4 443 881)				(1 270 976 - 1 328 846)
				11.08	13.56	2.48	CHF 1 756 374
				(10.28 - 11.78)	(12.57 - 14.42)	(2.29 - 2.65)	(1 639 638 - 1 896 302)
C: 4%	CHF 582 733	CHF 5 860 281	CHF 5 277 548	26.14	41.60	15.46	CHF 341 455
E: 1.5%	(507 199 - 660 903)	(5 766 916 - 5 953 056)	(5 152 658 - 5 401 237)				(333 375 - 349 458)
				18.42	29.27	10.84	CHF 487 201
				(17.13 - 19.53)	(27.22 - 31.03)	(10.08 - 11.53)	(456 727 - 522 392)

C: costs; E: effects; IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LY: life years; LYG: life-years gained; QALYs: quality-adjusted life years.

9.1.2.4 Impact quality of life

Figure 22, Table 44 and Table 45 show the results for the scenario analysis including the utility values per ppFEV1 category based on the study of Tappenden et al.[107] instead of Acaster et al..[105] Because of the higher utility values and the larger difference in utility values between the three ppFEV1 categories, the ICERs are better in the scenario using the utility values from Tappenden et al..[107] The ICERs decreased to about CHF1.4 million (HAS) and CHF1 million (ZIN) per QALY gained.

Figure 22: ICERs – impact quality of life (HAS & ZIN)



ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 44: IC, IE and ICERs – impact quality of life (HAS)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (CHF/LYG) ICER (CHF/QALY gained)
	mean	mean	mean	mean	mean	mean	mean
QoL	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)
Acaster et al.	CHF 861 982	CHF 7 399 751	CHF 6 537 769	22.95	28.34	5.39	CHF 1 213 756
	(751 897 - 979 228)	(7 268 189 - 7 529 035)	(6 363 152 - 6 713 133)				(1 181 338 - 1 246 313)
				16.17	20.21	4.04	CHF 1 620 029
				(15.04 - 17.14)	(18.77 - 21.47)	(3.70 - 4.35)	(1 496 608 - 1 761 751)
Tappenden et al.	CHF 861 982	CHF 7 399 751	CHF 6 537 769	22.95	28.34	5.39	CHF 1 213 756
	(751 897 - 979 228)	(7 268 189 - 7 529 035)	(6 363 152 - 6 713 133)				(1 181 338 - 1 246 313)
				18.76	23.44	4.68	CHF 1 398 662
				(17.15 - 20.01)	(21.42 - 25.00)	(4.25 - 5.05)	(1 285 431 - 1 541 398)

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LY: life years; LYG: life-years gained; QALYs: quality-adjusted life years.

Table 45: IC, IE and ICERs – impact quality of life (ZIN)

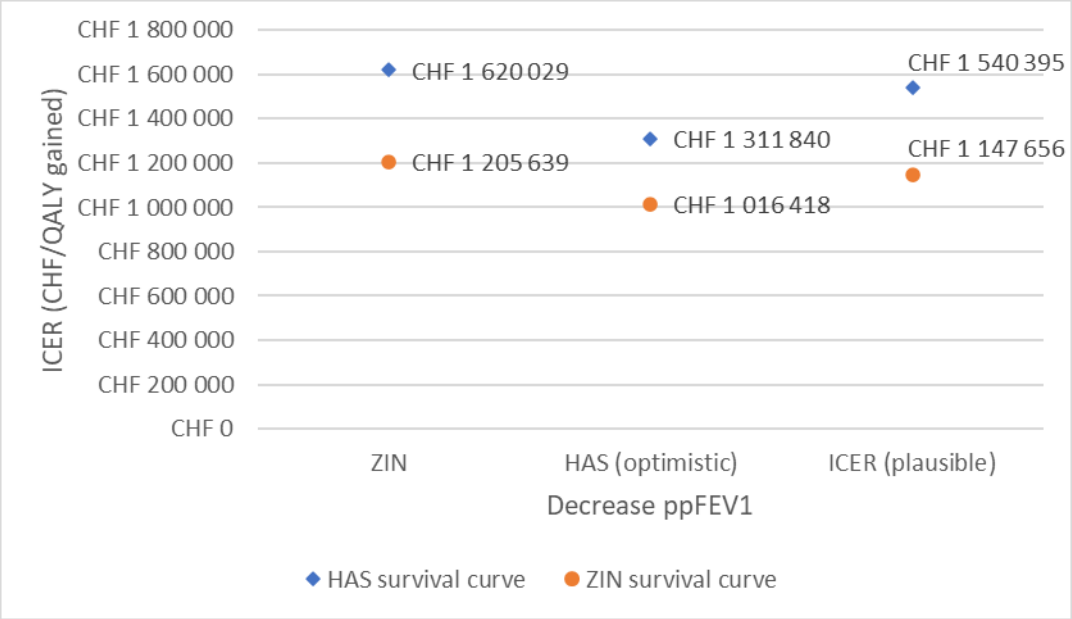
	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (CHF/LYG) ICER (CHF/QALY gained)
	mean	mean	mean	mean	mean	mean	mean
QoL	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)
Acaster et al.	CHF 710 727	CHF 7 329 176	CHF 6 618 450	20.43	28.08	7.65	CHF 865 450
	(619 212 - 808 900)	(7 202 041 - 7 457 212)	(6 452 513 - 6 778 058)				(843 752 - 886 321)
				14.51	20.01	5.50	CHF 1 205 639
				(13.48 - 15.41)	(18.59 - 21.24)	(5.10 - 5.85)	(1 127 235 - 1 296 594)
Tappenden et al.	CHF 710 727	CHF 7 329 176	CHF 6 618 450	20.43	28.08	7.65	CHF 865 450
	(619 212 - 808 900)	(7 202 041 - 7 457 212)	(6 452 513 - 6 778 058)				(843 752 - 886 321)
				16.83	23.21	6.37	CHF 1 039 882
				(15.40 - 17.93)	(21.22 - 24.76)	(5.83 - 6.80)	(964 516 - 1 138 215)

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LY: life years; LYG: life-years gained; QALYs: quality-adjusted life years.

9.1.2.5 Impact decrease ppFEV1

Figure 23, Table 46 and Table 47 show the results for the scenario analyses regarding the decrease in ppFEV1 in the comparator and intervention group. The results of the scenarios using inputs from the ZIN and ICER reports are close to each other. The most optimistic scenario from the HAS report with a stronger constraint in the decline of ppFEV1 in the intervention group leads to a lower ICER of about CHF1.3 million and CHF1 million per QALY gained when applying the HAS or ZIN survival curve for the comparator group, respectively.

Figure 23: ICERs – impact of the decrease in ppFEV1 (HAS & ZIN)



ICER: incremental cost-effectiveness ratio; ppFEV1: percentage predicted forced expiratory volume in the first second; QALYs: quality-adjusted life years.

Table 46: IC, IE and ICERs – impact of the decrease in ppFEV1 (HAS)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (CHF/LYG) ICER (CHF/QALY gained)
Decrease ppFEV1	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**
ZIN	CHF 861 982 (751 897 - 979 228)	CHF 7 399 751 (7 268 189 - 7 529 035)	CHF 6 537 769 (6 363 152 - 6 713 133)	22.95	28.34	5.39	CHF 1 213 756 (1 181 338 - 1 246 313)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 1 620 029 (1 496 608 - 1 761 751)
HAS (optimistic)	CHF 861 982 (751 897 - 979 228)	CHF 7 089 785 (6 984 760 - 7 191 779)	CHF 6 227 803 (6 058 891 - 6 393 475)	22.95	28.34	5.39	CHF 1 156 210 (1 124 851 - 1 186 967)
				16.17 (15.04 - 17.14)	20.93 (19.38 - 22.31)	4.76 (4.30 - 5.25)	CHF 1 311 840 (1 178 915 - 1 446 193)
ICER (plausible)	CHF 835 040 (722 552 - 952 339)	CHF 7 312 967 (7 194 645 - 7 438 047)	CHF 6 477 927 (6 303 826 - 6 644 039)	22.95	28.34	5.39	CHF 1 202 646 (1 170 324 - 1 233 485)
				16.27 (15.09 - 17.29)	20.48 (18.96 - 21.82)	4.21 (3.85 - 4.54)	CHF 1 540 395 (1 422 281 - 1 678 590)

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LY: life years; LYG: life-years gained; ppFEV1: percentage predicted forced expiratory volume in the first second; QALYs: quality-adjusted life years.

Table 47: IC, IE and ICERs – impact of the decrease in ppFEV1 (ZIN)

Decrease ppFEV1	Cost comparator mean (2.5% - 97.5%)	Cost intervention mean (2.5% - 97.5%)	Incremental cost mean (2.5% - 97.5%)	LYs comparator QALYs comparator mean (2.5% - 97.5%)	LYs intervention QALYs intervention mean (2.5% - 97.5%)	IE (LYG) IE (QALYs gained) mean (2.5% - 97.5%)	ICER (CHF/LYG) ICER (CHF/QALY gained) mean (2.5% - 97.5%)
ZIN	CHF 710 727 (619 212 - 808 900)	CHF 7 329 176 (7 202 041 - 7 457 212)	CHF 6 618 450 (6 452 513 - 6 778 058)	20.43	28.08	7.65	CHF 865 450 (843 752 - 886 321)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 1 205 639 (1 127 235 - 1 296 594)
HAS (optimistic)	CHF 710 727 (619 212 - 808 900)	CHF 7 023 988 (6 920 230 - 7 124 943)	CHF 6 313 261 (6 160 766 - 6 460 828)	20.43	28.08	7.65	CHF 825 543 (805 602 - 844 839)
				14.51 (13.48 - 15.41)	20.74 (19.20 - 22.10)	6.22 (5.70 - 6.74)	CHF 1 016 418 (931 323 - 1 103 185)
ICER (plausible)	CHF 694 581 (602 490 - 792 787)	CHF 7 246 245 (7 128 890 - 7 369 892)	CHF 6 551 664 (6 394 268 - 6 703 688)	20.43	28.08	7.65	CHF 856 717 (836 135 - 876 596)
				14.57 (13.51 - 15.50)	20.29 (18.78 - 21.61)	5.72 (5.27 - 6.12)	CHF 1 147 656 (1 069 498 - 1 234 369)

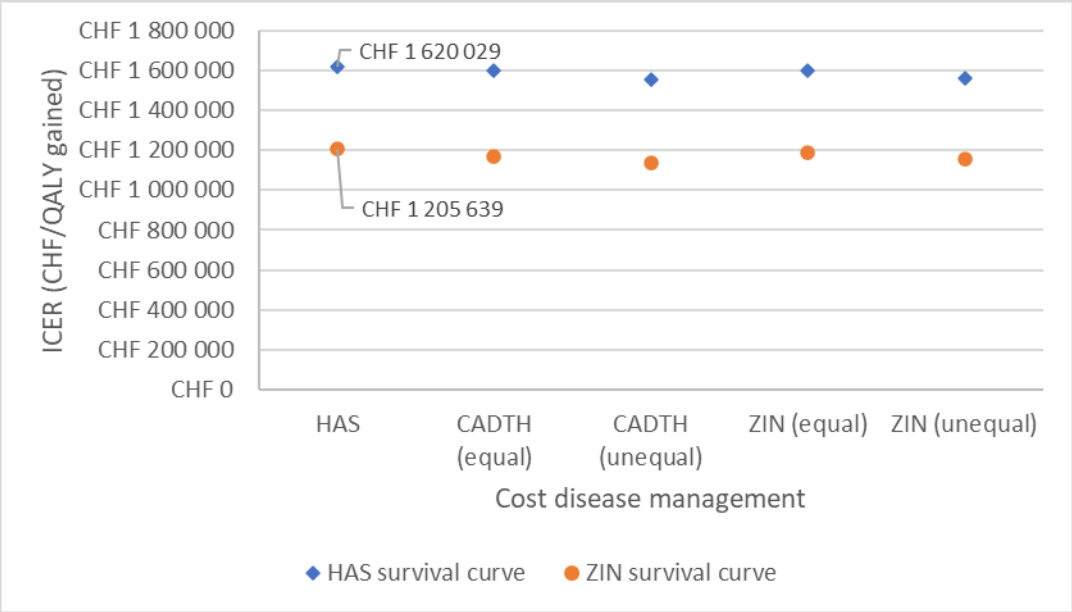
IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LY: life years; LYG: life-years gained; ppFEV1: percentage predicted forced expiratory volume in the first second; QALYs: quality-adjusted life years.

9.1.2.6 Impact disease management cost

Figure 24, Table 48, and Table 49 show the impact of different scenarios on disease management costs. A scenario with an unequal cost, where the cost per ppFEV1 category is lower for Trikafta®, gives the best results. However, it is worth noting that the impact on the ICER is relatively small. The reason is that the decrease in disease management costs is relatively small compared to the annual additional cost for Trikafta®. For example, in the 'CADTH unequal' scenario, the disease management cost for patients receiving Trikafta® is CHF6306 instead of CHF11 000 per year for patients with a ppFEV1 ≥70% (see Table 30). This contrasts with the yearly extra cost of about CHF228 000 for the drug.

Furthermore, we note that in the model, only from ppFEV1 <70% the costs for disease management increase a first time, and a second time if ppFEV1 <40%. It takes time in the model for the population to move to a lower ppFEV1 category given the annual modelled decline in ppFEV1 in the comparator and intervention group (see Table 23 and Table 24 in part 8.8.1.3). Even if the ppFEV1 drops from, e.g. 95% to 75%, this has no impact on the modelled disease management costs. We come back to this in the discussion.

Figure 24: ICERs – impact of the disease management cost (HAS & ZIN)



ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 48: IC, IE and ICERs – impact of the disease management cost (HAS)

Cost disease management	Cost comparator mean (2.5% - 97.5%)	Cost intervention mean (2.5% - 97.5%)	Incremental cost mean (2.5% - 97.5%)	LYs comparator QALYs comparator mean (2.5% - 97.5%)	LYs intervention QALYs intervention mean (2.5% - 97.5%)	IE (LYG) IE (QALYs gained) mean (2.5% - 97.5%)	ICER (CHF/LYG) ICER (CHF/QALY gained) mean (2.5% - 97.5%)
HAS	CHF 861 982 (751 897 - 979 228)	CHF 7 399 751 (7 268 189 - 7 529 035)	CHF 6 537 769 (6 363 152 - 6 713 133)	22.95	28.34	5.39	CHF 1 213 756 (1 181 338 - 1 246 313)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 1 620 029 (1 496 608 - 1 761 751)
CADTH (equal)	CHF 314 647 (278 025 - 351 611)	CHF 6 760 486 (6 713 800 - 6 808 564)	CHF 6 445 839 (6 380 121 - 6 509 928)	22.95	28.34	5.39	CHF 1 196 689 (1 184 488 - 1 208 587)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 1 597 281 (1 484 868 - 1 744 504)
CADTH (unequal)	CHF 314 621 (276 732 - 352 610)	CHF 6 587 793 (6 555 060 - 6 616 875)	CHF 6 273 173 (6 219 562 - 6 321 242)	22.95	28.34	5.39	CHF 1 164 633 (1 154 680 - 1 173 557)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 1 554 495 (1 440 131 - 1 693 295)
ZIN (equal)	CHF 697 355 (607 373 - 789 026)	CHF 7 161 196 (7 065 428 - 7 264 269)	CHF 6 463 840 (6 320 323 - 6 596 486)	22.95	28.34	5.39	CHF 1 200 031 (1 173 386 - 1 224 657)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 1 601 709 (1 484 577 - 1 745 531)
ZIN (unequal)	CHF 701 450 (615 029 - 785 511)	CHF 7 002 994 (6 925 550 - 7 075 243)	CHF 6 301 544 (6 180 635 - 6 416 507)	22.95	28.34	5.39	CHF 1 169 900 (1 147 453 - 1 191 243)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 1 561 525 (1 447 703 - 1 701 865)

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LY: life years; LYG: life-years gained; QALYs: quality-adjusted life years.

Table 49: IC, IE and ICERs – impact of the disease management cost (ZIN)

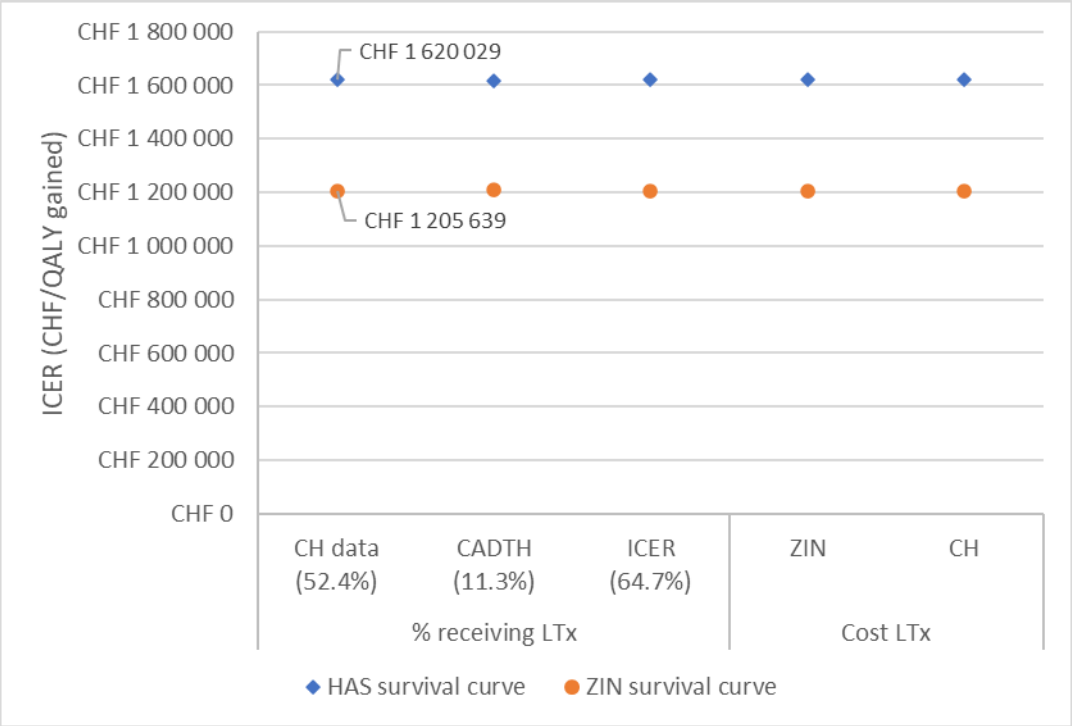
Cost disease management	Cost comparator mean (2.5% - 97.5%)	Cost intervention mean (2.5% - 97.5%)	Incremental cost mean (2.5% - 97.5%)	LYs comparator QALYs comparator mean (2.5% - 97.5%)	LYs intervention QALYs intervention mean (2.5% - 97.5%)	IE (LYG) IE (QALYs gained) mean (2.5% - 97.5%)	ICER (CHF/LYG) ICER (CHF/QALY gained) mean (2.5% - 97.5%)
HAS	CHF 710 727 (619 212 - 808 900)	CHF 7 329 176 (7 202 041 - 7 457 212)	CHF 6 618 450 (6 452 513 - 6 778 058)	20.43	28.08	7.65	CHF 865 450 (843 752 - 886 321)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 1 205 639 (1 127 235 - 1 296 594)
CADTH (equal)	CHF 273 587 (241 671 - 306 421)	CHF 6 694 089 (6 644 225 - 6 742 524)	CHF 6 420 501 (6 357 830 - 6 480 268)	20.43	28.08	7.65	CHF 839 566 (831 371 - 847 381)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 1 169 600 (1 097 346 - 1 260 881)
CADTH (unequal)	CHF 273 575 (240 460 - 305 843)	CHF 6 523 090 (6 485 356 - 6 554 326)	CHF 6 249 516 (6 198 571 - 6 294 587)	20.43	28.08	7.65	CHF 817 207 (810 545 - 823 101)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 1 138 451 (1 067 554 - 1 225 002)
ZIN (equal)	CHF 578 267 (506 275 - 654 635)	CHF 7 094 663 (7 001 496 - 7 195 024)	CHF 6 516 396 (6 388 067 - 6 637 261)	20.43	28.08	7.65	CHF 852 105 (835 325 - 867 910)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 1 187 051 (1 110 926 - 1 278 435)
ZIN (unequal)	CHF 581 514 (510 444 - 652 499)	CHF 6 937 469 (6 861 950 - 7 008 475)	CHF 6 355 955 (6 245 013 - 6 456 706)	20.43	28.08	7.65	CHF 831 125 (816 618 - 844 300)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 1 157 848 (1 086 525 - 1 249 170)

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LY: life years; LYG: life-years gained; QALYs: quality-adjusted life years.

9.1.2.7 Impact % receiving and cost of lung transplantation

Figure 25, Table 50 and Table 51 show the impact of the scenarios changing the percentage of patients receiving a lung transplant if ppFEV1 becomes <30%, as well as the impact of changing the lung transplant costs and/or follow-up costs. Based on the model calculations, the impact is negligible. The main reason is that lung transplantation is only considered at a ppFEV1 <30%. Based on the evolution in ppFEV1, this is only relatively late in the model (around the age of 40 years in the comparator group). As a result, there is a large impact of the discount rate. In addition, the lung transplant cost is also allocated only once to the percentage of patients receiving a lung transplant, after which the annual follow-up cost is taken into account. However, these costs are much lower than the annual cost for Trikafta®.

Figure 25: ICERs – impact of % receiving and cost lung transplantation (HAS & ZIN)



ICER: incremental cost-effectiveness ratio; LTx: lung transplantation; QALYs: quality-adjusted life years.

Table 50: IC, IE and ICERs – impact of % receiving and cost lung transplantation (HAS)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (CHF/LYG) ICER (CHF/QALY gained)
% receiving LTx	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**
CH data (52.4%)	CHF 861 982 (751 897 - 979 228)	CHF 7 399 751 (7 268 189 - 7 529 035)	CHF 6 537 769 (6 363 152 - 6 713 133)	22.95	28.34	5.39	CHF 1 213 756 (1 181 338 - 1 246 313)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 1 620 029 (1 496 608 - 1 761 751)
CADTH (11.3%)	CHF 870 067 (758 765 - 991 061)	CHF 7 415 114 (7 279 136 - 7 548 435)	CHF 6 545 048 (6 371 212 - 6 721 413)	22.95	28.34	5.39	CHF 1 215 107 (1 182 834 - 1 247 850)
				16.14 (15.01 - 17.12)	20.20 (18.76 - 21.45)	4.06 (3.71 - 4.36)	CHF 1 615 624 (1 493 015 - 1 753 302)
ICER (64.7%)	CHF 859 615 (751 058 - 976 904)	CHF 7 395 266 (7 265 593 - 7 525 349)	CHF 6 535 651 (6 360 015 - 6 707 246)	22.95	28.34	5.39	CHF 1 213 362 (1 180 755 - 1 245 220)
				16.18 (15.05 - 17.15)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.34)	CHF 1 621 340 (1 498 135 - 1 763 518)
Cost lung transplant	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**
ZIN	CHF 863 894 (753 763 - 981 924)	CHF 7 400 436 (7 268 766 - 7 529 331)	CHF 6 536 542 (6 362 950 - 6 712 045)	22.95	28.34	5.39	CHF 1 213 528 (1 181 300 - 1 246 111)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 1 619 724 (1 496 080 - 1 761 129)
CH	CHF 862 723 (752 611 - 980 248)	CHF 7 399 982 (7 268 355 - 7 529 134)	CHF 6 537 259 (6 362 962 - 6 712 572)	22.95	28.34	5.39	CHF 1 213 661 (1 181 302 - 1 246 208)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 1 619 902 (1 496 486 - 1 761 633)

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; ; LTx: lung transplantation; LY: life years; LYG: life-years gained; QALYs: quality-adjusted life years.

Table 51: IC, IE and ICERs – impact of % receiving and cost lung transplantation (ZIN)

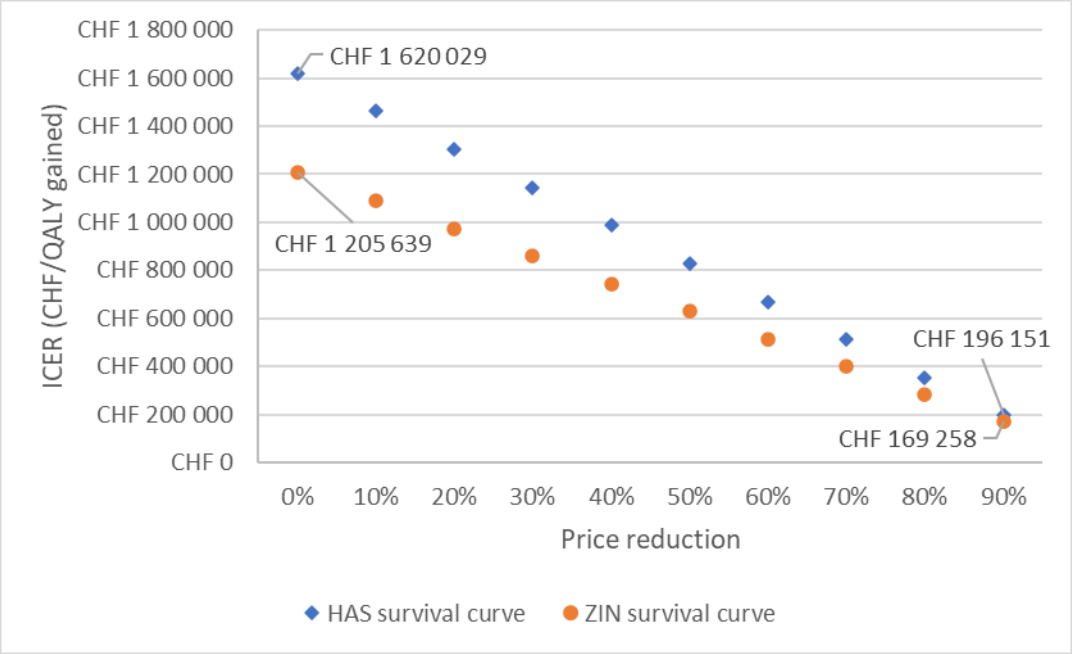
	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (CHF/LYG) ICER (CHF/QALY gained)
% receiving LTx	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**
CH data (52.4%)	CHF 710 727 (619 212 - 808 900)	CHF 7 329 176 (7 202 041 - 7 457 212)	CHF 6 618 450 (6 452 513 - 6 778 058)	20.43	28.08	7.65	CHF 865 450 (843 752 - 886 321)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 1 205 639 (1 127 235 - 1 296 594)
CADTH (11.3%)	CHF 715 164 (622 500 - 814 040)	CHF 7 349 063 (7 215 429 - 7 479 341)	CHF 6 633 899 (6 473 195 - 6 796 250)	20.43	28.08	7.65	CHF 867 470 (846 456 - 888 700)
				14.50 (13.47 - 15.40)	20.00 (18.58 - 21.22)	5.50 (5.10 - 5.85)	CHF 1 208 239 (1 129 608 - 1 298 244)
ICER (64.7%)	CHF 709 427 (618 038 - 806 529)	CHF 7 323 365 (7 196 898 - 7 450 657)	CHF 6 613 938 (6 449 116 - 6 773 370)	20.43	28.08	7.65	CHF 864 860 (843 307 - 885 708)
				14.52 (13.49 - 15.41)	20.01 (18.59 - 21.25)	5.50 (5.10 - 5.85)	CHF 1 204 884 (1 127 056 - 1 296 053)
Cost lung transplant	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**	**mean (2.5% - 97.5%)**
ZIN	CHF 711 778 (619 930 - 810 582)	CHF 7 330 040 (7 202 361 - 7 457 883)	CHF 6 618 262 (6 452 550 - 6 777 800)	20.43	28.08	7.65	CHF 865 426 (843 757 - 886 287)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 1 205 605 (1 127 147 - 1 296 533)
CH	CHF 711 126 (619 418 - 809 423)	CHF 7 329 457 (7 202 145 - 7 457 418)	CHF 6 618 331 (6 452 418 - 6 777 901)	20.43	28.08	7.65	CHF 865 435 (843 739 - 886 300)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 1 205 618 (1 127 209 - 1 296 571)

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; ; LTx: lung transplantation; LY: life years; LYG: life-years gained; QALYs: quality-adjusted life years.

9.1.2.8 Impact price reduction Trikafta®

Figure 26, Table 52 and Table 53 show the impact of a price reduction of Trikafta® on the ICERs. This was applied to the scenario whose inputs are summarised in Table 22 in combination with a hazard ratio of 0.1. With a 90% price reduction, i.e. with a Trikafta® cost of about CHF23 000 per patient annually, the average ICER is reduced from about CHF1.6 million and CHF1.2 million per QALY gained to less than CHF200 000 or CHF170 000 per QALY gained, in the HAS and ZIN scenarios, respectively.

Figure 26: ICERs – impact of % price reduction Trikafta® (HAS & ZIN)



ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 52: IC, IE and ICERs – impact of % price reduction Trikafta® (HAS)

Price discount	Cost comparator mean (2.5% - 97.5%)	Cost intervention mean (2.5% - 97.5%)	Incremental cost mean (2.5% - 97.5%)	LYs comparator QALYs comparator mean (2.5% - 97.5%)	LYs intervention QALYs intervention mean (2.5% - 97.5%)	IE (LYG) IE (QALYs gained) mean (2.5% - 97.5%)	ICER (CHF/LYG) ICER (CHF/QALY gained) mean (2.5% - 97.5%)
0%	CHF 861 982 (751 897 - 979 228)	CHF 7 399 751 (7 268 189 - 7 529 035)	CHF 6 537 769 (6 363 152 - 6 713 133)	22.95	28.34	5.39	CHF 1 213 756 (1 181 338 - 1 246 313)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 1 620 029 (1 496 608 - 1 761 751)
10%	CHF 861 982 (751 897 - 979 228)	CHF 6 761 300 (6 629 346 - 6 889 721)	CHF 5 899 318 (5 725 411 - 6 074 498)	22.95	28.34	5.39	CHF 1 095 226 (1 062 939 - 1 127 748)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 1 461 820 (1 349 030 - 1 590 359)
20%	CHF 861 982 (751 897 - 979 228)	CHF 6 122 849 (5 990 613 - 6 252 145)	CHF 5 260 867 (5 088 531 - 5 436 087)	22.95	28.34	5.39	CHF 976 695 (944 700 - 1 009 225)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 1 303 611 (1 201 644 - 1 418 777)
30%	CHF 861 982 (751 897 - 979 228)	CHF 5 484 398 (5 352 089 - 5 613 887)	CHF 4 622 416 (4 450 820 - 4 797 280)	22.95	28.34	5.39	CHF 858 165 (826 308 - 890 629)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 1 145 403 (1 055 319 - 1 248 410)
40%	CHF 861 982 (751 897 - 979 228)	CHF 4 845 947 (4 713 161 - 4 975 339)	CHF 3 983 965 (3 812 055 - 4 158 615)	22.95	28.34	5.39	CHF 739 635 (707 719 - 772 059)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 987 194 (908 336 - 1 077 433)

Price discount	Cost comparator mean (2.5% - 97.5%)	Cost intervention mean (2.5% - 97.5%)	Incremental cost mean (2.5% - 97.5%)	LYs comparator QALYs comparator mean (2.5% - 97.5%)	LYs intervention QALYs intervention mean (2.5% - 97.5%)	IE (LYG) IE (QALYs gained) mean (2.5% - 97.5%)	ICER (CHF/LYG) ICER (CHF/QALY gained) mean (2.5% - 97.5%)
50%	CHF 861 982 (751 897 - 979 228)	CHF 4 207 496 (4 074 378 - 4 336 835)	CHF 3 345 514 (3 173 279 - 3 520 576)	22.95	28.34	5.39	CHF 621 104 (589 128 - 653 605)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 828 986 (760 412 - 909 542)
60%	CHF 861 982 (751 897 - 979 228)	CHF 3 569 045 (3 435 732 - 3 699 375)	CHF 2 707 063 (2 534 503 - 2 881 482)	22.95	28.34	5.39	CHF 502 574 (470 538 - 534 955)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 670 777 (609 000 - 740 619)
70%	CHF 861 982 (751 897 - 979 228)	CHF 2 930 594 (2 796 880 - 3 061 095)	CHF 2 068 612 (1 895 727 - 2 242 712)	22.95	28.34	5.39	CHF 384 044 (351 947 - 416 366)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 512 568 (457 833 - 573 649)
80%	CHF 861 982 (751 897 - 979 228)	CHF 2 292 143 (2 157 680 - 2 423 886)	CHF 1 430 161 (1 256 975 - 1 604 060)	22.95	28.34	5.39	CHF 265 514 (233 361 - 297 798)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 354 360 (305 989 - 406 626)
90%	CHF 861 982 (751 897 - 979 228)	CHF 1 653 692 (1 518 486 - 1 785 330)	CHF 791 710 (618 252 - 965 340)	22.95	28.34	5.39	CHF 146 983 (114 780 - 179 218)
				16.17 (15.04 - 17.14)	20.21 (18.77 - 21.47)	4.04 (3.70 - 4.35)	CHF 196 151 (151 725 - 241 531)

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LY: life years; LYG: life-years gained; QALYs: quality-adjusted life years.

Table 53: IC, IE and ICERs – impact of % price reduction Trikafta® (ZIN)

Price discount	Cost comparator mean (2.5% - 97.5%)	Cost intervention mean (2.5% - 97.5%)	Incremental cost mean (2.5% - 97.5%)	LYs comparator QALYs comparator mean (2.5% - 97.5%)	LYs intervention QALYs intervention mean (2.5% - 97.5%)	IE (LYG) IE (QALYs gained) mean (2.5% - 97.5%)	ICER (CHF/LYG) ICER (CHF/QALY gained) mean (2.5% - 97.5%)
0%	CHF 710 727 (619 212 - 808 900)	CHF 7 329 176 (7 202 041 - 7 457 212)	CHF 6 618 450 (6 452 513 - 6 778 058)	20.43	28.08	7.65	CHF 865 450 (843 752 - 886 321)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 1 205 639 (1 127 235 - 1 296 594)
10%	CHF 710 727 (619 212 - 808 900)	CHF 6 697 043 (6 568 400 - 6 824 772)	CHF 5 986 316 (5 820 813 - 6 146 203)	20.43	28.08	7.65	CHF 782 790 (761 149 - 803 698)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 1 090 486 (1 019 199 - 1 173 148)
20%	CHF 710 727 (619 212 - 808 900)	CHF 6 064 910 (5 935 465 - 6 192 385)	CHF 5 354 183 (5 188 052 - 5 514 379)	20.43	28.08	7.65	CHF 700 130 (678 407 - 721 078)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 975 332 (910 858 - 1 050 583)
30%	CHF 710 727 (619 212 - 808 900)	CHF 5 432 777 (5 302 227 - 5 559 633)	CHF 4 722 050 (4 557 229 - 4 882 182)	20.43	28.08	7.65	CHF 617 471 (595 918 - 638 410)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 860 179 (802 000 - 928 862)
40%	CHF 710 727 (619 212 - 808 900)	CHF 4 800 644 (4 670 455 - 4 927 787)	CHF 4 089 917 (3 926 169 - 4 250 695)	20.43	28.08	7.65	CHF 534 811 (513 399 - 555 835)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 745 026 (692 137 - 807 162)

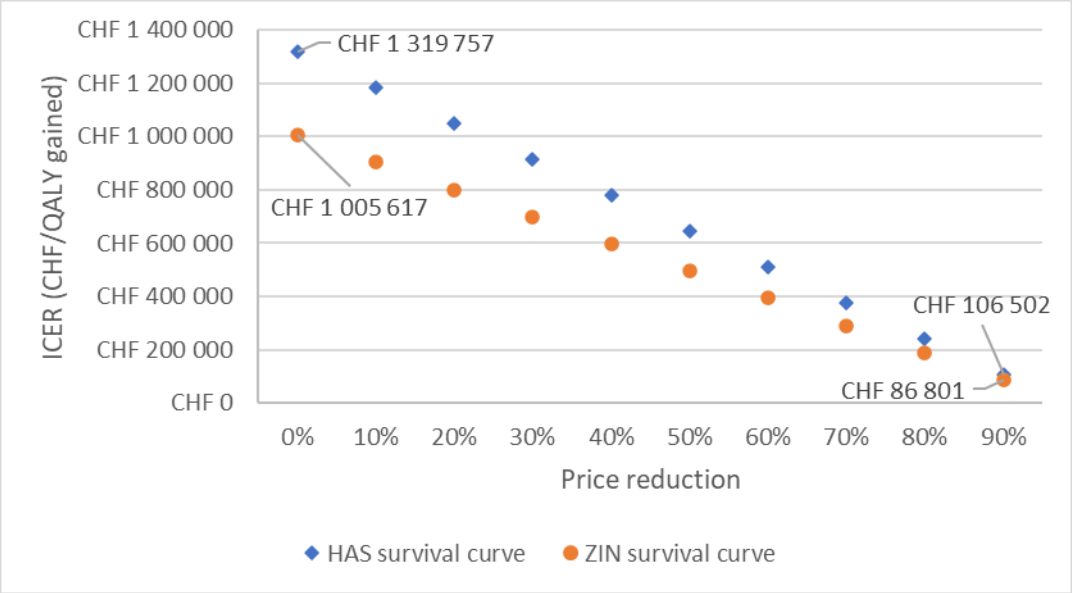
Price discount	Cost comparator mean (2.5% - 97.5%)	Cost intervention mean (2.5% - 97.5%)	Incremental cost mean (2.5% - 97.5%)	LYs comparator QALYs comparator mean (2.5% - 97.5%)	LYs intervention QALYs intervention mean (2.5% - 97.5%)	IE (LYG) IE (QALYs gained) mean (2.5% - 97.5%)	ICER (CHF/LYG) ICER (CHF/QALY gained) mean (2.5% - 97.5%)
50%	CHF 710 727 (619 212 - 808 900)	CHF 4 168 510 (4 037 773 - 4 295 998)	CHF 3 457 784 (3 294 236 - 3 618 595)	20.43	28.08	7.65	CHF 452 151 (430 765 - 473 179)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 629 872 (582 261 - 684 588)
60%	CHF 710 727 (619 212 - 808 900)	CHF 3 536 377 (3 405 880 - 3 664 417)	CHF 2 825 650 (2 663 573 - 2 986 357)	20.43	28.08	7.65	CHF 369 491 (348 298 - 390 506)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 514 719 (473 008 - 561 294)
70%	CHF 710 727 (619 212 - 808 900)	CHF 2 904 244 (2 772 848 - 3 033 563)	CHF 2 193 517 (2 032 354 - 2 354 119)	20.43	28.08	7.65	CHF 286 831 (265 757 - 307 832)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 399 565 (362 914 - 440 320)
80%	CHF 710 727 (619 212 - 808 900)	CHF 2 272 111 (2 139 746 - 2 400 484)	CHF 1 561 384 (1 400 107 - 1 722 550)	20.43	28.08	7.65	CHF 204 172 (183 083 - 225 246)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 284 412 (251 699 - 320 155)
90%	CHF 710 727 (619 212 - 808 900)	CHF 1 639 978 (1 507 228 - 1 769 568)	CHF 929 251 (769 134 - 1 090 669)	20.43	28.08	7.65	CHF 121 512 (100 574 - 142 620)
				14.51 (13.48 - 15.41)	20.01 (18.59 - 21.24)	5.50 (5.10 - 5.85)	CHF 169 258 (140 253 - 200 082)

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LY: life years; LYG: life-years gained; QALYs: quality-adjusted life years.

9.1.2.9 Impact price reduction Trikafta® – ‘optimal’ scenario

In addition, another scenario is developed in which the most optimistic scenarios are combined into an 'optimal' scenario. In this scenario, the assumption of a hazard ratio of 0.1 was kept and combined with the HAS 'optimistic' scenario for the evolution in ppFEV1 (see Table 24) and the CADTH 'unequal' scenario for the disease management costs (see Table 30). The results are shown in Figure 27, Table 54 and Table 55. Applying this ‘optimal’ scenario reduced the ICERs to about CHF1.3 million and CHF1 million per QALY gained for the HAS and ZIN scenarios, respectively. Applying a price discount of 90% in this ‘optimal’ scenario, an ICER of about CHF107 000 or CHF87 000 per QALY gained is obtained in the HAS and ZIN scenarios, respectively.

Figure 27: ICERs – impact of % price reduction Trikafta® – ‘optimal’ scenario (HAS & ZIN)



ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 54: IC, IE and ICERs – impact of % price reduction Trikafta® – 'optimal' scenario (HAS)

Price discount	Cost comparator mean (2.5% - 97.5%)	Cost intervention mean (2.5% - 97.5%)	Incremental cost mean (2.5% - 97.5%)	LYs comparator QALYs comparator mean (2.5% - 97.5%)	LYs intervention QALYs intervention mean (2.5% - 97.5%)	IE (LYG) IE (QALYs gained) mean (2.5% - 97.5%)	ICER (CHF/LYG) ICER (CHF/QALY gained) mean (2.5% - 97.5%)
0%	CHF 314 621 (276 732 - 352 610)	CHF 6 580 073 (6 553 025 - 6 607 403)	CHF 6 265 452 (6 218 650 - 6 312 471)	22.95	28.34	5.39	CHF 1 163 199 (1 154 510 - 1 171 928)
				16.17 (15.04 - 17.14)	20.93 (19.38 - 22.31)	4.76 (4.30 - 5.25)	CHF 1 319 757 (1 193 927 - 1 462 508)
10%	CHF 314 621 (276 732 - 352 610)	CHF 5 940 088 (5 913 040 - 5 967 418)	CHF 5 625 467 (5 578 665 - 5 672 486)	22.95	28.34	5.39	CHF 1 044 384 (1 035 695 - 1 053 113)
				16.17 (15.04 - 17.14)	20.93 (19.38 - 22.31)	4.76 (4.30 - 5.25)	CHF 1 184 951 (1 072 454 - 1 313 622)
20%	CHF 314 621 (276 732 - 352 610)	CHF 5 300 103 (5 273 056 - 5 327 433)	CHF 4 985 482 (4 938 680 - 5 032 501)	22.95	28.34	5.39	CHF 925 569 (916 880 - 934 298)
				16.17 (15.04 - 17.14)	20.93 (19.38 - 22.31)	4.76 (4.30 - 5.25)	CHF 1 050 145 (950 897 - 1 164 565)
30%	CHF 314 621 (276 732 - 352 610)	CHF 4 660 118 (4 633 071 - 4 687 448)	CHF 4 345 497 (4 298 696 - 4 392 516)	22.95	28.34	5.39	CHF 806 754 (798 065 - 815 483)
				16.17 (15.04 - 17.14)	20.93 (19.38 - 22.31)	4.76 (4.30 - 5.25)	CHF 915 339 (829 259 - 1 014 947)
40%	CHF 314 621 (276 732 - 352 610)	CHF 4 020 133 (3 993 086 - 4 047 463)	CHF 3 705 512 (3 658 711 - 3 752 531)	22.95	28.34	5.39	CHF 687 939 (679 250 - 696 668)
				16.17 (15.04 - 17.14)	20.93 (19.38 - 22.31)	4.76 (4.30 - 5.25)	CHF 780 533 (707 060 - 865 243)

Price discount	Cost comparator mean (2.5% - 97.5%)	Cost intervention mean (2.5% - 97.5%)	Incremental cost mean (2.5% - 97.5%)	LYs comparator QALYs comparator mean (2.5% - 97.5%)	LYs intervention QALYs intervention mean (2.5% - 97.5%)	IE (LYG) IE (QALYs gained) mean (2.5% - 97.5%)	ICER (CHF/LYG) ICER (CHF/QALY gained) mean (2.5% - 97.5%)
50%	CHF 314 621 (276 732 - 352 610)	CHF 3 380 148 (3 353 101 - 3 407 478)	CHF 3 065 528 (3 018 726 - 3 112 546)	22.95	28.34	5.39	CHF 569 124 (560 435 - 577 853)
				16.17 (15.04 - 17.14)	20.93 (19.38 - 22.31)	4.76 (4.30 - 5.25)	CHF 645 726 (584 193 - 715 540)
60%	CHF 314 621 (276 732 - 352 610)	CHF 2 740 164 (2 713 116 - 2 767 493)	CHF 2 425 543 (2 378 741 - 2 472 561)	22.95	28.34	5.39	CHF 450 309 (441 620 - 459 038)
				16.17 (15.04 - 17.14)	20.93 (19.38 - 22.31)	4.76 (4.30 - 5.25)	CHF 510 920 (460 858 - 566 810)
70%	CHF 314 621 (276 732 - 352 610)	CHF 2 100 179 (2 073 131 - 2 127 508)	CHF 1 785 558 (1 738 756 - 1 832 577)	22.95	28.34	5.39	CHF 331 494 (322 805 - 340 223)
				16.17 (15.04 - 17.14)	20.93 (19.38 - 22.31)	4.76 (4.30 - 5.25)	CHF 376 114 (337 995 - 416 931)
80%	CHF 314 621 (276 732 - 352 610)	CHF 1 460 194 (1 433 146 - 1 487 523)	CHF 1 145 573 (1 098 771 - 1 192 592)	22.95	28.34	5.39	CHF 212 679 (203 990 - 221 408)
				16.17 (15.04 - 17.14)	20.93 (19.38 - 22.31)	4.76 (4.30 - 5.25)	CHF 241 308 (215 908 - 269 259)
90%	CHF 314 621 (276 732 - 352 610)	CHF 820 209 (793 161 - 847 539)	CHF 505 588 (458 786 - 552 607)	22.95	28.34	5.39	CHF 93 864 (85 175 - 102 593)
				16.17 (15.04 - 17.14)	20.93 (19.38 - 22.31)	4.76 (4.30 - 5.25)	CHF 106 502 (93 044 - 122 247)

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LY: life years; LYG: life-years gained; QALYs: quality-adjusted life years.

Table 55: IC, IE and ICERs – impact of % price reduction Trikafta® – 'optimal' scenario (ZIN)

Price discount	Cost comparator mean (2.5% - 97.5%)	Cost intervention mean (2.5% - 97.5%)	Incremental cost mean (2.5% - 97.5%)	LYs comparator QALYs comparator mean (2.5% - 97.5%)	LYs intervention QALYs intervention mean (2.5% - 97.5%)	IE (LYG) IE (QALYs gained) mean (2.5% - 97.5%)	ICER (CHF/LYG) ICER (CHF/QALY gained) mean (2.5% - 97.5%)
0%	CHF 273 575 (240 460 - 305 843)	CHF 6 519 715 (6 492 970 - 6 546 805)	CHF 6 246 141 (6 204 084 - 6 288 480)	20.43	28.08	7.65	CHF 816 766 (811 266 - 822 302)
				14.51 (13.48 - 15.41)	20.74 (19.20 - 22.10)	6.22 (5.70 - 6.74)	CHF 1 005 617 (923 115 - 1 094 730)
10%	CHF 273 575 (240 460 - 305 843)	CHF 5 885 603 (5 858 858 - 5 912 693)	CHF 5 612 029 (5 569 972 - 5 654 368)	20.43	28.08	7.65	CHF 733 847 (728 348 - 739 384)
				14.51 (13.48 - 15.41)	20.74 (19.20 - 22.10)	6.22 (5.70 - 6.74)	CHF 903 526 (829 387 - 983 345)
20%	CHF 273 575 (240 460 - 305 843)	CHF 5 251 491 (5 224 746 - 5 278 581)	CHF 4 977 917 (4 935 860 - 5 020 256)	20.43	28.08	7.65	CHF 650 929 (645 429 - 656 465)
				14.51 (13.48 - 15.41)	20.74 (19.20 - 22.10)	6.22 (5.70 - 6.74)	CHF 801 435 (735 656 - 872 381)
30%	CHF 273 575 (240 460 - 305 843)	CHF 4 617 380 (4 590 634 - 4 644 469)	CHF 4 343 805 (4 301 748 - 4 386 144)	20.43	28.08	7.65	CHF 568 010 (562 511 - 573 547)
				14.51 (13.48 - 15.41)	20.74 (19.20 - 22.10)	6.22 (5.70 - 6.74)	CHF 699 345 (641 925 - 761 727)
40%	CHF 273 575 (240 460 - 305 843)	CHF 3 983 268 (3 956 522 - 4 010 357)	CHF 3 709 693 (3 667 637 - 3 752 032)	20.43	28.08	7.65	CHF 485 092 (479 592 - 490 628)
				14.51 (13.48 - 15.41)	20.74 (19.20 - 22.10)	6.22 (5.70 - 6.74)	CHF 597 254 (548 198 - 650 118)

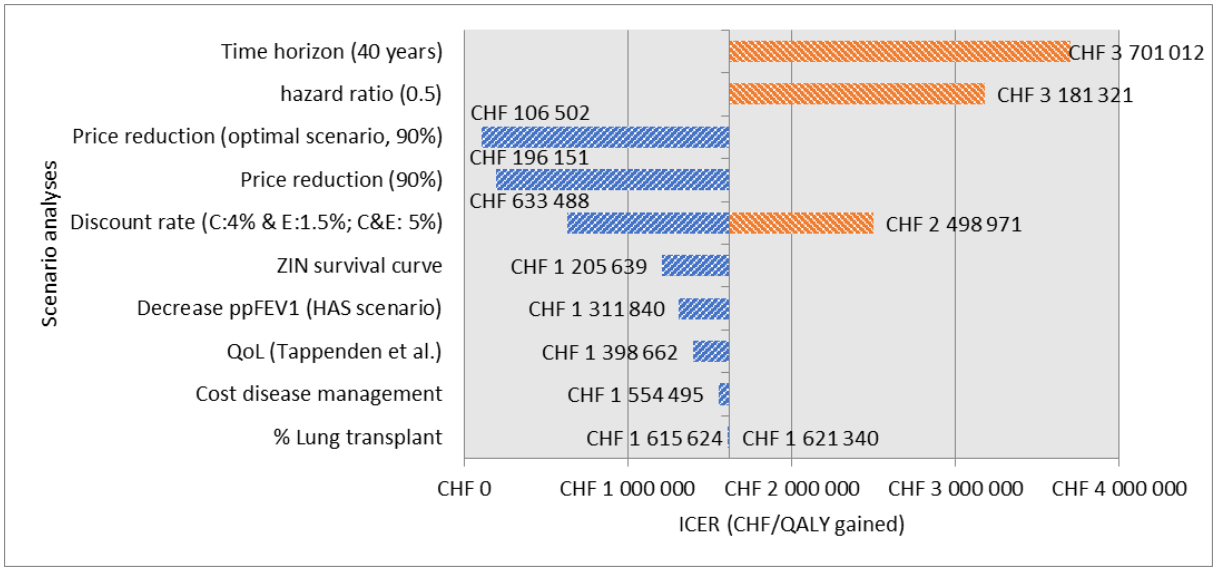
Price discount	Cost comparator mean (2.5% - 97.5%)	Cost intervention mean (2.5% - 97.5%)	Incremental cost mean (2.5% - 97.5%)	LYs comparator QALYs comparator mean (2.5% - 97.5%)	LYs intervention QALYs intervention mean (2.5% - 97.5%)	IE (LYG) IE (QALYs gained) mean (2.5% - 97.5%)	ICER (CHF/LYG) ICER (CHF/QALY gained) mean (2.5% - 97.5%)
50%	CHF 273 575 (240 460 - 305 843)	CHF 3 349 156 (3 322 410 - 3 376 245)	CHF 3 075 581 (3 033 525 - 3 117 920)	20.43	28.08	7.65	CHF 402 173 (396 674 - 407 709)
				14.51 (13.48 - 15.41)	20.74 (19.20 - 22.10)	6.22 (5.70 - 6.74)	CHF 495 163 (454 471 - 539 182)
60%	CHF 273 575 (240 460 - 305 843)	CHF 2 715 044 (2 688 298 - 2 742 133)	CHF 2 441 469 (2 399 413 - 2 483 808)	20.43	28.08	7.65	CHF 319 254 (313 755 - 324 791)
				14.51 (13.48 - 15.41)	20.74 (19.20 - 22.10)	6.22 (5.70 - 6.74)	CHF 393 073 (360 751 - 428 905)
70%	CHF 273 575 (240 460 - 305 843)	CHF 2 080 932 (2 054 186 - 2 108 021)	CHF 1 807 357 (1 765 301 - 1 849 696)	20.43	28.08	7.65	CHF 236 336 (230 836 - 241 872)
				14.51 (13.48 - 15.41)	20.74 (19.20 - 22.10)	6.22 (5.70 - 6.74)	CHF 290 982 (267 035 - 318 167)
80%	CHF 273 575 (240 460 - 305 843)	CHF 1 446 820 (1 420 074 - 1 473 909)	CHF 1 173 245 (1 131 189 - 1 215 584)	20.43	28.08	7.65	CHF 153 417 (147 918 - 158 954)
				14.51 (13.48 - 15.41)	20.74 (19.20 - 22.10)	6.22 (5.70 - 6.74)	CHF 188 891 (172 584 - 207 499)
90%	CHF 273 575 (240 460 - 305 843)	CHF 812 708 (785 962 - 839 797)	CHF 539 133 (497 077 - 581 472)	20.43	28.08	7.65	CHF 70 499 (64 999 - 76 035)
				14.51 (13.48 - 15.41)	20.74 (19.20 - 22.10)	6.22 (5.70 - 6.74)	CHF 86 801 (77 655 - 97 363)

IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LY: life years; LYG: life-years gained; QALYs: quality-adjusted life years.

9.1.3 Deterministic sensitivity analyses

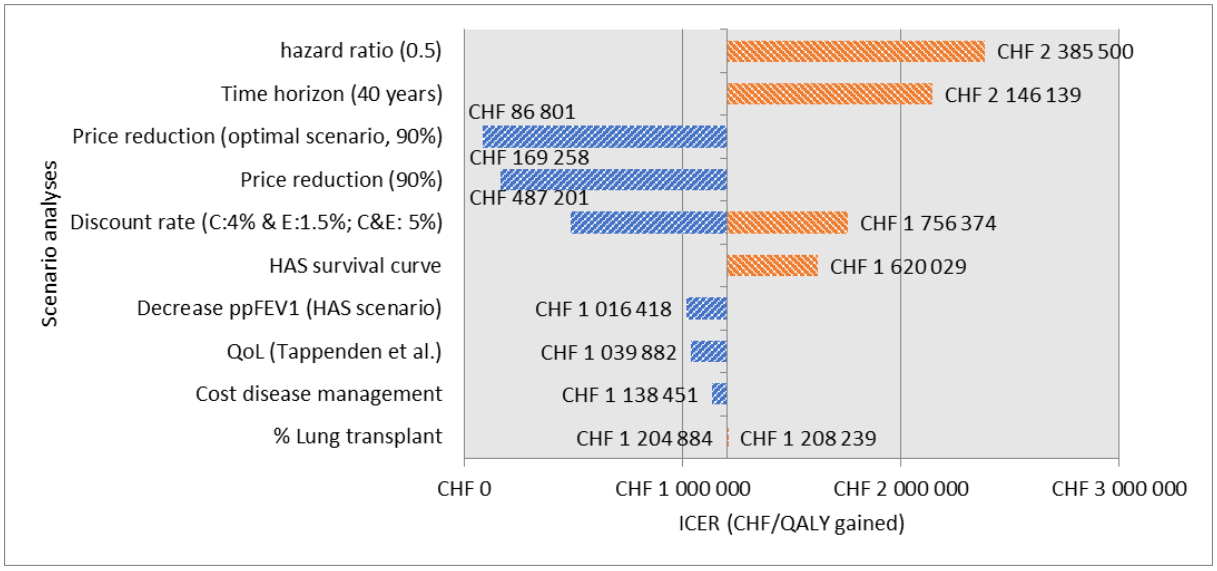
Figure 28 and Figure 29 show the results of the scenario analyses in a tornado graph. Because of the price of Trikafta® and its chronic use, the price reduction is decisive in achieving lower ICERs. As soon as a lower hazard ratio or a shorter time horizon is applied, the ICERs increase. In line with the time horizon, the discount rate applied is also very influential.

Figure 28: Tornado graph (HAS)



ICER: incremental cost-effectiveness ratio; ppFEV1: percentage predicted forced expiratory volume in the first second; QALYs: quality-adjusted life years. The 'base-case' ICER in the above figure is CHF1 620 029 per QALY gained.

Figure 29: Tornado graph (ZIN)



ICER: incremental cost-effectiveness ratio; ppFEV1: percentage predicted forced expiratory volume in the first second; QALYs: quality-adjusted life years. The 'base-case' ICER in the above figure is CHF1 205 639 per QALY gained.

9.2 Budget impact analysis

There are arguments both in favour of assuming equal and unequal disease management costs. Instead of presenting one scenario as the base case and the other as a scenario analysis, both scenarios are presented in a neutral way without making any value judgement on which is the most probable.

9.2.1 Equal disease management costs

Table 56 presents the costs from the model for patients aged 6-11 years old in a scenario with equal costs per ppFEV1 category. In the intervention group, the most important cost is related to Trikafta®: on average CHF226 861 per patient. The follow-up cost is negligible. The disease management cost does not vary much over the years as most patients remain within the same ppFEV1 category during the first years in the model. The disease management cost in the comparator group is about the same since proportionally not many more patients evolved into a lower ppFEV1 category during the first years of the model compared to the intervention group.

Table 56: Budget impact per patient – age 6-11 years (equal cost per ppFEV1 category)

	Intervention			Comparator
Age	Cost Trikafta®*	Cost FU	Cost disease management**	Cost disease management**
6 years	CHF226 952	CHF437	CHF17 469	CHF17 473
7 years	CHF226 926	CHF14	CHF17 539	CHF17 559
8 years	CHF226 890	CHF14	CHF17 593	CHF17 629
9 years	CHF226 845	CHF14	CHF17 646	CHF17 734
10 years	CHF226 801	CHF14	CHF17 712	CHF17 869
11 years	CHF226 751	CHF14	CHF17 793	CHF17 993
Average	**CHF226 861**	**CHF85**	**CHF17 625**	**CHF17 710**

FU: follow-up; ppFEV1: percentage predicted forced expiratory volume in the first second. * The small change over the years is caused by the minimal mortality that was present in the model for ages 6-11 in the intervention group (<0.1% in the scenario with a hazard ratio of 0.1). ** Based on the disease management costs from the HAS scenario in Table 30.

For the total budget impact for homozygous patients aged 6-11 years, the cost per patient from Table 56 is applied to the 69 patients. The total budget impact over 5 years for Trikafta® at the official list price is about CHF78 million (Table 57, part a - 1st level). The impact at the 2nd level is the same as the disease management costs in the intervention and comparator group neutralise

each other. The third level takes into account the use of Orkambi® and Symdeko®, bringing the total 5-year budget impact back to CHF55 million for 69 F508del homozygous patients.

Table 58 (part a) shows the same calculation for the 70 F508del heterozygous patients aged 6-11 years. The total budget impact over 5 years is about CHF79 million. Taking into account the substitution costs for Kalydeco®, this becomes about CHF78 million.

Combining the results for both F508del homozygous and heterozygous patients aged 6-11 years results in a total budget impact over 5 years of CHF158 million for Trikafta® on the 1st or 2nd level or CHF133 million on the 3rd level.

Next to the patients aged 6-11 years, there is also the potential budget impact for treating patients ≥12 years. Table 57 (part b) shows that treating 305 homozygous patients could result in a 5-year budget impact of CHF348 million for Trikafta®. After exclusion of the substitution costs, this becomes about CHF342 million. Table 58 (part b) presents the results for treating yearly 266 heterozygous patients. This results in a 5-year budget impact of about CHF304 million or CHF290 million, without or with extraction of the substitution costs, respectively.

Combining the data for all patients (6-11 years and ≥12 years) results in the following total 5-year budget impact:

- Homozygous patients (n = 69 + 305 = 374): CHF426 million (1st level) or CHF397 million (3rd level)
- Heterozygous patients (n = 70 + 266 = 336): CHF383 million (1st level) or CHF368 million (3rd level)

Table 57: Total budget impact over 5 years for F508del homozygous patients (equal cost per ppFEV1 category)

a) age 6-11 years (homozygous)

Budget impact per year		**(6-11 years)**	Intervention			Comparator	
Year	Market penetration	N° of patients	Total cost Trikafta®	Total FU cost	Total cost disease management	Total cost disease management	Total cost Kalydeco® Orkambi® and Symdeko® *
1	100%	69	CHF 15 653 401	CHF 5 836	CHF 1 216 145	CHF 1 221 958	CHF 4 641 542
2	100%	69	CHF 15 653 401	CHF 5 836	CHF 1 216 145	CHF 1 221 958	CHF 4 641 542
3	100%	69	CHF 15 653 401	CHF 5 836	CHF 1 216 145	CHF 1 221 958	CHF 4 641 542
4	100%	69	CHF 15 653 401	CHF 5 836	CHF 1 216 145	CHF 1 221 958	CHF 4 641 542
5	100%	69	CHF 15 653 401	CHF 5 836	CHF 1 216 145	CHF 1 221 958	CHF 4 641 542
Total budget impact over 5 years							
1st level	CHF 78 267 006		CHF 78 267 006				
2nd level	CHF 78 267 121		CHF 78 267 006	CHF 29 178	CHF 6 080 727	CHF 6 109 789	
3rd level	CHF 55 059 411		CHF 78 267 006	CHF 29 178	CHF 6 080 727	CHF 6 109 789	CHF 23 207 710

ppFEV1: percentage predicted forced expiratory volume in the first second. * (29 x CHF138 746 (Orkambi®)) + (4 x CHF154 477 (Symdeko®)) = CHF4 641 542.

b) age ≥12 years (homozygous)

Budget impact per year		**(≥12 years)**	Intervention			Comparator	
Year	Market penetration	N° of patients	Total cost Trikafta®	Total FU cost	Total cost disease management	Total cost disease management	Total cost Kalydeco® Orkambi® and Symdeko® *
1	100%	305	CHF 69 642 480	/	/	/	CHF 1 327 369
2	100%	305	CHF 69 642 480	/	/	/	CHF 1 327 369
3	100%	305	CHF 69 642 480	/	/	/	CHF 1 327 369
4	100%	305	CHF 69 642 480	/	/	/	CHF 1 327 369
5	100%	305	CHF 69 642 480	/	/	/	CHF 1 327 369
Total budget impact over 5 years							
1st level	CHF 348 212 400		CHF 348 212 400				
2nd level	/		/	/	/	/	
3rd level	CHF 341 575 555		CHF 348 212 400	/	/	/	CHF 6 636 845

* (4 x CHF138 746 (Orkambi®)) + (5 x CHF154 477 (Symdeko®)) = CHF1 327 369.

Table 58: Total budget impact over 5 years for F508del heterozygous patients (equal cost per ppFEV1 category)

a) age 6-11 years (heterozygous)

Budget impact per year		**(6-11 years)**	Intervention			Comparator	
Year	Market penetration	N° of patients	Total cost Trikafta®	Total FU cost	Total cost disease management	Total cost disease management	Total cost Kalydeco® Orkambi® and Symdeko® *
1	100%	70	CHF 15 880 262	CHF 5 920	CHF 1 233 771	CHF 1 239 667	CHF 353 576
2	100%	70	CHF 15 880 262	CHF 5 920	CHF 1 233 771	CHF 1 239 667	CHF 353 576
3	100%	70	CHF 15 880 262	CHF 5 920	CHF 1 233 771	CHF 1 239 667	CHF 353 576
4	100%	70	CHF 15 880 262	CHF 5 920	CHF 1 233 771	CHF 1 239 667	CHF 353 576
5	100%	70	CHF 15 880 262	CHF 5 920	CHF 1 233 771	CHF 1 239 667	CHF 353 576
Total budget impact over 5 years							
1st level	CHF 79 401 310		CHF 79 401 310				
2nd level	CHF 79 401 428		CHF 79 401 310	CHF 29 600	CHF 6 168 853	CHF 6 198 337	
3rd level	CHF 77 633 548		CHF 79 401 310	CHF 29 600	CHF 6 168 853	CHF 6 198 337	CHF 1 767 880

ppFEV1: percentage predicted forced expiratory volume in the first second. * 2 x CHF176 788 (Kalydeco®)) = CHF353 576.

b) age ≥12 years (heterozygous)

Budget impact per year		**(≥12 years)**	Intervention			Comparator	
Year	Market penetration	N° of patients	Total cost Trikafta®	Total FU cost	Total cost disease management	Total cost disease management	Total cost Kalydeco® Orkambi® and Symdeko® *
1	100%	266	CHF 60 737 376	/	/	/	CHF 2 761 675
2	100%	266	CHF 60 737 376	/	/	/	CHF 2 761 675
3	100%	266	CHF 60 737 376	/	/	/	CHF 2 761 675
4	100%	266	CHF 60 737 376	/	/	/	CHF 2 761 675
5	100%	266	CHF 60 737 376	/	/	/	CHF 2 761 675
Total budget impact over 5 years							
1st level	CHF 303 686 880		CHF 303 686 880				
2nd level	/		/	/	/	/	
3rd level	CHF 289 878 505		CHF 303 686 880	/	/	/	CHF 13 808 375

* (3 x CHF154 477 (Symdeko®)) + (13 x CHF176 788 (Kalydeco®)) = CHF2 761 675.

9.2.2 Unequal disease management costs

Table 59 presents the costs from the model for patients aged 6-11 years old in a scenario with lower costs per ppFEV1 category in the intervention group. The costs associated with Trikafta® remain the same as in Table 56. In the 'unequal' scenario, the disease management costs associated with the intervention group are almost CHF5000 lower than in the comparator group.

Table 59: Budget impact per patient – age 6-11 years (unequal cost per ppFEV1 category)

	Intervention			Comparator
Age	Cost Trikafta®*	Cost FU	Cost disease management**	Cost disease management**
6 years	CHF226 952	CHF437	CHF6471	CHF11 361
7 years	CHF226 926	CHF14	CHF6483	CHF11 394
8 years	CHF226 890	CHF14	CHF6491	CHF11 420
9 years	CHF226 845	CHF14	CHF6499	CHF11 459
10 years	CHF226 801	CHF14	CHF6510	CHF11 512
11 years	CHF226 751	CHF14	CHF6522	CHF11 559
Average	**CHF226 861**	**CHF85**	**CHF6496**	**CHF11 451**

FU: follow-up; ppFEV1: percentage predicted forced expiratory volume in the first second. * The small change over the years is caused by the minimal mortality that was present in the model for ages 6-11 in the intervention group (<0.1% in the scenario with a hazard ratio of 0.1). ** Based on the disease management costs from the CADTH scenario in Table 30 with lower costs for patients receiving CFTR modulators.

Table 60 and Table 61 show the total budget impact over 5 years for the F508del homozygous and heterozygous patients, respectively. Compared with the 'equal' disease management cost scenario, the budget impact at the 2nd level is reduced by about CHF1.7 million in both the homozygous and heterozygous groups aged 6-11 years.

In the 'unequal' disease management cost scenario, combining the results of both F508del homozygous and heterozygous patients results in a total budget impact over 5 years of CHF158 million for Trikafta® on the 1st level, CHF154 million on the 2nd level, or CHF129 million on the 3rd level for patients aged 6-11 years.

No follow-up or disease management costs were included for patients aged ≥12 years. As a result, the 5-year budget impact does not differ between the scenarios including an equal or unequal cost per ppFEV1 category. Therefore, we refer to the information presented in part 9.2.1.

Combining the data for all patients (6-11 years and ≥12 years) results in the following total 5-year budget impact:

- Homozygous patients (n = 69 + 305 = 374): CHF426 million (1st level) or CHF395 million (3rd level)
- Heterozygous patients (n = 70 + 266 = 336): CHF383 million (1st level) or CHF366 million (3rd level)

Table 60: Total budget impact over 5 years for F508del homozygous patients (unequal cost per ppFEV1 category)

a) age 6-11 years (homozygous)

Budget impact per year		**(6-11 years)**	Intervention			Comparator	
Year	Market penetration	N° of patients	Total cost Trikafta®	Total FU cost	Total cost disease management	Total cost disease management	Total cost Kalydeco® Orkambi® and Symdeko® *
1	100%	69	CHF 15 653 401	CHF 5 836	CHF 448 224	CHF 790 117	CHF 4 641 542
2	100%	69	CHF 15 653 401	CHF 5 836	CHF 448 224	CHF 790 117	CHF 4 641 542
3	100%	69	CHF 15 653 401	CHF 5 836	CHF 448 224	CHF 790 117	CHF 4 641 542
4	100%	69	CHF 15 653 401	CHF 5 836	CHF 448 224	CHF 790 117	CHF 4 641 542
5	100%	69	CHF 15 653 401	CHF 5 836	CHF 448 224	CHF 790 117	CHF 4 641 542
Total budget impact over 5 years							
1st level	CHF 78 267 006		CHF 78 267 006				
2nd level	CHF 76 586 721		CHF 78 267 006	CHF 29 178	CHF 2 241 121	CHF 3 950 584	
3rd level	CHF 53 379 011		CHF 78 267 006	CHF 29 178	CHF 2 241 121	CHF 3 950 584	CHF 23 207 710

ppFEV1: percentage predicted forced expiratory volume in the first second. * (29 x CHF138 746 (Orkambi®)) + (4 x CHF154 477 (Symdeko®)) = CHF4 641 542.

b) age ≥12 years (homozygous)

Same data as presented in Table 57 b)

Table 61: Total budget impact over 5 years for F508del heterozygous patients (unequal cost per ppFEV1 category)

a) age 6-11 years (heterozygous)

Budget impact per year		**(6-11 years)**	Intervention			Comparator	
Year	Market penetration	N° of patients	Total cost Trikafta®	Total FU cost	Total cost disease management	Total cost disease management	Total cost Kalydeco® Orkambi® and Symdeko® *
1	100%	70	CHF 15 880 262	CHF 5 920	CHF 454 720	CHF 801 568	CHF 353 576
2	100%	70	CHF 15 880 262	CHF 5 920	CHF 454 720	CHF 801 568	CHF 353 576
3	100%	70	CHF 15 880 262	CHF 5 920	CHF 454 720	CHF 801 568	CHF 353 576
4	100%	70	CHF 15 880 262	CHF 5 920	CHF 454 720	CHF 801 568	CHF 353 576
5	100%	70	CHF 15 880 262	CHF 5 920	CHF 454 720	CHF 801 568	CHF 353 576
Total budget impact over 5 years							
1st level	CHF 79 401 310		CHF 79 401 310				
2nd level	CHF 77 696 673		CHF 79 401 310	CHF 29 600	CHF 2 273 601	CHF 4 007 839	
3rd level	CHF 75 928 793		CHF 79 401 310	CHF 29 600	CHF 2 273 601	CHF 4 007 839	CHF 1 767 880

ppFEV1: percentage predicted forced expiratory volume in the first second. * 2 x CHF176 788 (Kalydeco®)) = CHF353 576.

b) age ≥12 years (heterozygous)

Same data as presented in Table 58 b)

10. Discussion

10.1 Clinical evidence

The systematic review of the clinical evidence identified three RCTs that compared Trikafta® with placebo in patients aged 6 and older with cystic fibrosis who have one F508del mutation and one minimal function mutation in the CFTR gene (F/MF).[29-31] No RCTs were published that compared Trikafta® with standard of care (placebo) in patients aged 6 and older with cystic fibrosis who are homozygous for F508del mutation (F/F), who have one F508del mutation and one residual function mutation in the CFTR gene (F/RF), or who have one F508del mutation and one gating mutation in the CFTR gene (F/G).

One RCT only included children aged 6-11 years,[30] a second (phase 2) RCT only included adults (aged at least 18 years),[29] while the third RCT included both children (aged at least 12 years) and adults.[31] In the latter RCT subgroup analyses were reported for some outcomes for patients aged 12-18 years and for patients aged 18 years and above.

Across the three RCTs consistent evidence of high-quality was found about the efficacy of Trikafta® regarding all relevant outcomes, i.e. ppFEV1, lung clearance index, pulmonary exacerbations, body mass index, weight, quality of life and sweat chloride. These positive effects were regardless of age, i.e. both in children aged 6 years and above, adolescents and adults.

The included RCTs reported the effects of Trikafta® up to 24 weeks. RCTs with a longer follow-up period are not yet available, but an open-label extension of study VX17-445-102[31] and VX17-445-103[34] provided non-randomized follow-up data up to 48 weeks.[41] In this study 506 participants (399 with F/MF mutation, 107 with F/F mutation) aged 12 years and older received Trikafta®. Among the F/MF participants, the estimated pulmonary exacerbation rate was 0.30 (95%CI 0.24-0.39) at 48 weeks.[41] A similar event rate was reported for F/F participants (0.30; 95%CI 0.20-0.45). Among the F/MF participants, the mean absolute changes from baseline in ppFEV1 at week 24 were 14.9 (95%CI 13.5-16.3) and 14.3 (95%CI 12.9-15.7) percentage points in those who had been in the placebo (N=189) or ELX/TEZ/IVA (N=180) groups, respectively, in the F/MF pivotal study.[41] In F/F participants, the mean absolute changes from baseline in ppFEV1 at week 36 were 12.8 (95%CI 10.1-15.4) and 11.9 (95%CI 9.3-14.5) percentage points in those who had been in the TEZ/IVA (N=49) or ELX/TEZ/IVA (N=51) groups, respectively, in the F/F pivotal study.[41]

Although no RCTs were found for homozygous patients, ICER was able to perform a network meta-analysis for ppFEV1 and the CFQ-R respiratory domain score using the results of study VX17-445-103 (comparing Trikafta® with Symdeko®)[34] and study VX14-661-106 (comparing Symdeko® with placebo).[58] For both outcomes, a significant effect was found in favour of Trikafta®.

Trikafta® was found to be safe and well tolerated. Serious adverse events and withdrawal due to adverse events were rare in the included studies. Most of the reported adverse events are related

with the underlying disease, i.e. cystic fibrosis. Adverse events that warrant attention are psychiatric disorders, headache and gastrointestinal symptoms because of frequency, and rash, hepatic adverse events and distal intestinal obstruction syndrome because of severity.

The findings of our clinical evidence review are highly consistent with those of the included systematic reviews and HTA reports.[4, 5, 17-25]

10.2 Exploratory economic evaluation

When presenting the results of the economic evaluation, it was stated that due to the lack of hard evidence about the impact of the intervention on both survival and quality of life, many assumptions were made and results should therefore be interpreted with caution. Given the lack of evidence to prefer one scenario over another, the results are presented side by side without any value judgment as to which scenario is more likely than another. In first instance, results are presented applying different hazard ratios for mortality (ranging from 1 to 0.1). For practical reasons, all other scenarios were only presented applying the hazard ratio of 0.1. Notwithstanding this large uncertainty, the analyses clearly show the most determining variables for the cost-effectiveness and possible impact and direction in which the ICERs evolve if other assumptions are adopted.

If we compare our results with those of previous HTA reports, the **QALYs gained** are close to those of previous analyses. In the scenario with a mortality HR of 0.1, we obtain 4.0 (HAS[g]) or 5.5 (ZIN[g]) QALYs gained. This is with a discount rate of 3% and is close to the QALYs gained from the ICER report where a discount rate of 3% was also applied: 5 (F/F), 5.3 (F/MF) or 5.8 (F/RF) QALYs gained (see Table 20). If a discount rate of 1.5% was applied, the QALYs gained in our model became 8.3 (HAS) or 10.8 (ZIN) (see Table 42 and Table 43). This is close to the 10.4 QALYs gained in the INESSS report that most likely also uses a discount rate of 1.5%.[h] In CADTH's analysis, the QALYs gained are somewhat lower: 4.2 (F/RF), 5.9 (F/MF), 6.3 (F/G) or 6.9 (F/F). The HAS report used a discount rate of 2.5% that gradually reduced to 1.5% after 30 years. Their analysis reports 7.2 QALYs gained (F/F). Given that these results are close to the QALYs gained in our model with a mortality hazard ratio of 0.1, this shows that a very large impact on mortality was assumed via the micro-simulation applied in the previous models.

The **incremental cost** in the model is about CHF6.2 (HAS) or CHF6.6 (ZIN) million. These incremental costs are also relatively high in three of the four identified HTA reports. The incremental cost is lower in the HAS report that uses a shorter time horizon of 40 years (see Table 20).

[g] As indicated in the methodology, two survival curves were modelled for the comparator group, one from the HAS report and another from the ZIN report. To make the distinction between these scenarios clear, this is indicated in the reporting by stating (HAS) or (ZIN) between brackets.

[h] According to the Canadian guidelines, in the reference case, an annual discount rate of 1.5% is applied to both costs and outcomes. (source: Guidelines for the Economic Evaluation of Health Technologies: Canada. 4th Edition. July 2017)

With an assumed mortality hazard ratio of 0.1, **the ICER** is about CHF1.6 (HAS) and CHF1.2 (ZIN) million per QALY gained. With the exception of the results from the HAS analysis (which nevertheless applies a shorter time horizon), and taking into account the difference in the discount rate, this does not contradict previous results. The **most determining variable** for these ICERs is also clear in all analyses: the yearly cost of Trikafta®. Besides this recurrent cost, the most determining variables for the ICERs are the applied time horizon, the mortality hazard ratio and the discount rate. A shorter time horizon of e.g. 40 years or a mortality hazard ratio of e.g. 0.5 strongly increases the ICERs. A price discount of about 90% is needed to get the ICERs in the neighbourhood of about CHF200 000 or CHF170 000 per QALY gained in the originally modelled HAS and ZIN scenarios, respectively (see part 9.1.2.8). With a 90% price discount, this becomes about CHF107 000 or CHF87 000 per QALY gained, respectively, applying an 'optimal' scenario (see part 9.1.2.9). The scenario analyses also show that, although to a lesser extent, the applied survival curve for the comparator group and the impact on quality of life are important determinants of the ICER.

In previous models set up by the manufacturer, a patient-level microsimulation model was used in which **mortality** was estimated based on a comparison with values for several variables such as age, ppFEV1, gender, weight-for-age z score, pancreatic sufficiency, diabetes mellitus, Staphylococcus aureus infection, Burkerholderia cepacian infection, and annual number of acute pulmonary exacerbations. Previous models required adjustment factors, which were not published transparently (see part 7.2.2.3), to reflect mortality in the control group correctly. There is great uncertainty about the impact of Trikafta® on the long-term course of the individual variables included in the microsimulation. Thus, automatically, there is also great uncertainty regarding the modelled impact of the intervention on mortality. To make this explicit, we chose to present the results for different mortality hazard ratios. Even with a significantly improved mortality hazard ratio, the ICER remains relatively high. The main explanation for this is the annual cost for Trikafta® combined with its recurrent use.

The (impact on) mortality was modelled as simply but also as transparent as possible because of the lack of good evidence regarding the impact of Trikafta® on this important variable. In our model, in a first step, mortality for the comparator group was based on survival curves presented in the HAS and ZIN reports. In a second step, hypothetical mortality hazard ratios were applied in different scenarios. Thereafter, survivors were classified into different ppFEV1 categories. The simplicity of the model has its limitations. For example, general mortality for the whole population is modelled not taking into account increased/reduced mortality reflecting individual patient characteristics. As a consequence, there might be an overrepresentation of patients with a worse ppFEV1 category since at the individual patient level you would expect these patients to have a higher probability of dying than patients with a better ppFEV1, and vice versa. Since the deterioration in ppFEV1 is more rapid in the comparator group, this possibly means that this particularly affects outcomes in the comparator group more negatively and possibly underestimates ICERs. The size of this impact

is difficult to estimate but may be limited due to the high impact of the discount rate on longer-term outcomes.

The **evolution in ppFEV1** is an important variable in the model since costs and effects are linked in the model through different ppFEV1 categories. There is however considerable uncertainty about the impact on the evolution in ppFEV1. This is reflected by the widely varying choices made in previous HTA reports about the reduction in the decline of ppFEV1: CADTH:[4] 0-80%; HAS:[62] 90%; ICER:[5] 50% as a plausible assumption in addition to another favourable and unfavourable assumption (see part 7.2.2.5). Results from modelling with the assumptions made in the ZIN report or the ICER 'plausible' scenario were not far from each other. However, applying the HAS 'optimistic' scenario improved the results, while ICERs remained above CHF1 million per QALY gained (see Figure 23). Better evidence on the (long-term) ppFEV1 evolution when using Trikafta® would provide support for better cost-effectiveness calculations.

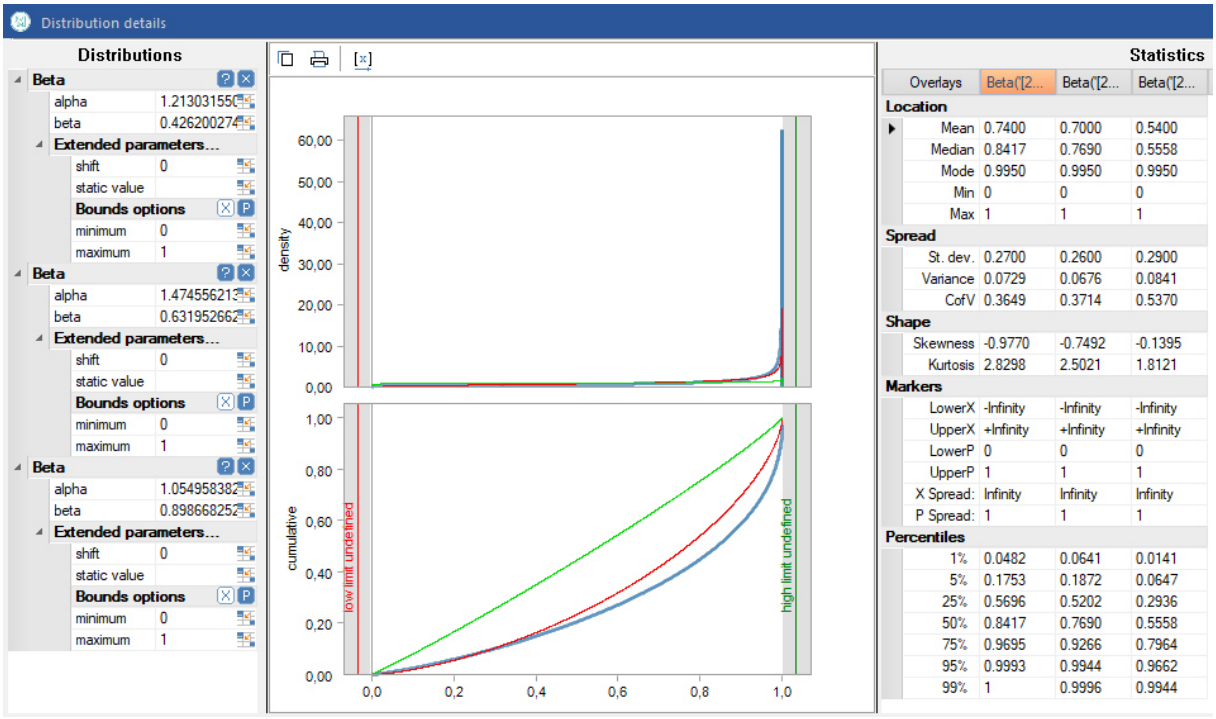
Another limitation is the **lack of genotype-specific evidence**. The survival curves of the comparator group are not available for the separate genotypes. While the evidence in the clinical section of this report refers to RCTs for the F/MF population, the information on survival in the comparator group, disease management costs or quality of life are based on a CF population in which the different genotypes are represented. Due to a lack of genotype-specific evidence, we were unable to perform subgroup analyses for the different genotypes. Looking at the identified economic evaluations, the CADTH report states that the F/RF genotype is a milder form of disease and therefore a slower rate of decline in ppFEV1 is assumed.[4] In the CADTH report, this leads to higher ICERs for this group (CAD2.4 million versus CAD1.4-1.7 million per QALY gained for the other three groups). In contrast, in the other reports, the ICERs are similar for the different genotypes. The authors of the INESSS report do not consider it appropriate for their evaluation to perform separate subgroup analyses, although they state confidence in clinical inputs to vary according to genotype.

Next, there is also a high uncertainty about the impact on **quality of life**. Previous HTA assessors have already indicated that the measurement of utilities based on a generic instrument (e.g., the EQ-5D) is lacking in the identified RCTs. As a second-best solution, EQ-5D utility scores were included in the model by linking them to the FEV1 levels. First, we used the EQ-5D utility scores stratified by FEV1 level published by Acaster et al..[105] In addition to this study, we also used the utilities used by Tappenden et al..[107] However, the utilities in Acaster's study are directly linked to the three FEV1 categories and therefore receive our preference.

However, there was a **problem in modelling the utilities** by using the published mean and standard deviation. We demonstrate this using the print screen of the ModelRisk® software. Figure 30 presents the probability distributions of the three beta distributions for the three utilities: 0.74 (0.27), 0.70 (0.26) and 0.54 (0.29). A beta distribution with these values can only be modelled with a very

broad distribution where most of the values are close to 1. If these distributions are modelled independently, about 2/3 of 1000 simulations yield illogical results where utilities for a better health state are lower than utilities in a worse health state. It is only logical if 'utility ppFEV1 ≥70%' > 'utility ppFEV1 ≥40 to <70%' > 'utility ppFEV1 <40%'. To obtain this, two **corrections were applied**: 1) the standard deviation was divided by 10 and 2) a correlation was introduced between draws for the utilities in the two highest ppFEV1 categories. For the beta distributions based on the publication of Tappenden et al.,[107] the standard deviation was already much smaller and it was only necessary to introduce a correlation between the two highest ppFEV1 categories. We note that in the HAS report, the three utilities were modelled as a beta distribution with overlapping confidence intervals: ppFEV1 ≥70%: 0.74 (0.592-0.888); ppFEV1 ≥40 to <70%: 0.70 (0.560-0.840); and ppFEV1 <40%: 0.54 (0.432-0.648). It is not clear how the problem of illogical draws from these probability distributions was addressed in other evaluations.

Figure 30: Problem with (uncorrected) modelling of utilities for ppFEV1 health states



Source: print screen from ModelRisk® software. The information shows the mean and standard deviation are correct. However, independent modelling of these three probability distributions does not always result in logical outcomes in which 'utility ppFEV1 ≥70%' > 'utility ppFEV1 ≥40 to <70%' > 'utility ppFEV1 <40%'. This is corrected in the model by reducing the standard deviation and including a correlation between the probability distributions.

Measuring quality of life in the randomised studies, with both disease-specific and generic utility instruments as recommended by the European network for Health Technology Assessment (EUnetHTA) guidelines for measuring quality of life,[123] would allow further refinement of the model. In the current model, there is an impact on quality of life only when patients drop from the 'ppFEV1 ≥70%' category to the 'ppFEV1 ≥40 to <70%' category, or later on to 'ppFEV1 <40%'. If utilities were determined for more specific ppFEV1 categories, smaller/earlier improvements in quality of

life could be included in the model. Due to the lack of using generic utility instruments, such reliable information is missing. As stated by the HAS assessors: "in the context of a chronic disease where symptoms considerably alter patients' quality of life, and where one of the aims of treatment is to improve quality of life, a robust estimate of utility scores is essential."[62]

The model could also be refined with **better information about the impact on disease management costs**. We did not identify reliable information for Switzerland for all disease management costs. A Swiss study on "Direct medical costs of cystic fibrosis in Switzerland" was identified and the principal investigator was contacted, but the publication of the results was not (yet) available at the time of drafting this report. However, cost information was obtained through FOPH for lung transplantation and pulmonary exacerbations. The Swiss costs for lung transplantation were in between the costs modelled in the 'Whiting' and 'ZIN' scenario (see Table 31). The scenario analyses showed that the impact of this cost is minimal (Figure 25) as this event occurs relatively late in the model resulting in a large impact of the discount rate. In addition, the cost of the lung transplantation itself can be considered large. But relatively speaking, this non-recurrent cost for lung transplantation is lower than the annual cost for Trikafta®, which dominates the impact on the ICER.

It is difficult to determine whether the disease management costs from the foreign studies are representative for Switzerland. Therefore, several scenarios were developed based on information available in previous HTA reports where a worse ppFEV1 category is associated with higher disease management costs (see Table 30). Scenarios were also modelled where costs within each ppFEV1 category are lower for the group using Trikafta®. Again, the impact on ICERs is limited (see Figure 24) because of the relatively smaller disease management cost that can be saved compared to the annual additional cost of Trikafta®.

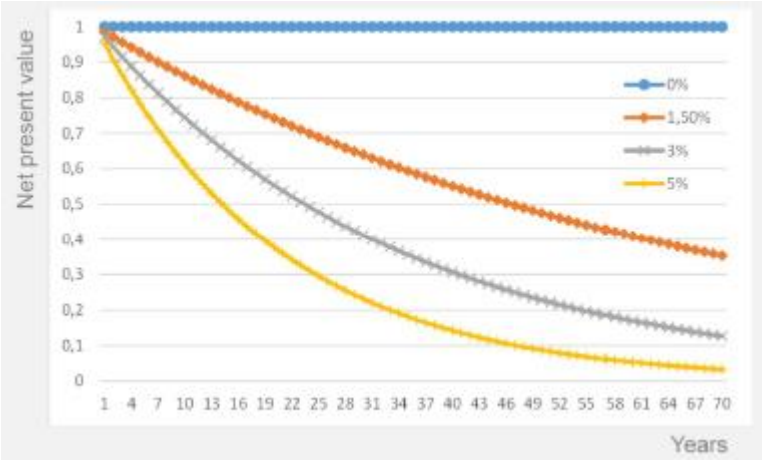
We would like to point at the **danger of possible double counting**. In the economic evaluations, cost and quality of life are modelled by ppFEV1 categories. In addition, reference is also made to e.g. the impact of pulmonary exacerbations on both costs and quality of life. However, the description of disease management costs in previous reports indicates that costs for pulmonary exacerbations are already included in the disease management costs. The data from the QoL study from Acaster et al.[105] also show that a large part of the population (30.1%) recently had an exacerbation (see part 8.8.2). Therefore, the results of this study are already influenced by the occurrence of exacerbations. People with a worse ppFEV1 value have a higher probability of being confronted with exacerbations and a worse QoL is already reflected in the different ppFEV1 categories. The manufacturer also awarded an additional QoL benefit to patients taking Trikafta® (see Table 19 in part 7.2.2.6) because of the gain in QoL 'unrelated to respiratory benefits'. The HAS assessors have already remarked that the EQ-5D questionnaire already considers these benefits. The separate inclusion of these additional benefits on costs and/or effects might point at double counting, which should be avoided in an economic evaluation. Further research could examine how costs

and quality of life evolve across ppFEV1 categories, and how Trikafta® affects these outcomes in the short and long term.

The main determinant of incremental costs is the **price of Trikafta®** because of both the annual cost of the product and the reciprocal nature of this expense due to its chronic use. It is the main variable through which ICER can be significantly reduced (see Figure 28 and Figure 29). Information was received about the possibility of reducing the costs for children with a weight <30kg by prescribing the adult dose and only giving half of it, because the paediatric dose is exactly the same price as the adult dose but contains only half the active ingredient (see Table 27), which can easily be halved. Reference was made to a case study mentioning crushing tablets does not compromise the product's clinical efficacy and may be valuable in some rare, difficult situations.[124] The article also refers to the drug's leaflet, which mentions that the tablets must not be chewed, crushed or broken before swallowing. However, we note that the 50% savings still means that the yearly cost is about CHF114 000 per person. Furthermore, it is important to note that children soon weigh more than 30kg. In Study 116,[30] including patients aged 6-11 years, 64% (77/121) weighed less than 30kg. In adolescents, this usually is not the case anymore. With this chronic treatment, the adult dose is given quickly to everyone. Therefore, this way of reducing costs will not have the same impact as a general price negotiation for all patients receiving this chronic treatment. The price discounts recommended in other reports are also much higher than 50%. For example, in the CADTH report, "the committee recommended reimbursement of [Trikafta®] with conditions, including a price reduction of 90%."[4]

Differences in the **discount rate** have a considerable influence on the incremental impact of future costs and effects, and thus the ICER.[125] As shown by the following figure from the EUnetHTA guidance document for economic evaluations, the net present value is very sensitive to a changing discount rate. However, the discount rate for costs and effects is not an input variable that may be applied arbitrarily. It should be applied according to national guidelines. In this case, FOPH has indicated in advance to apply an equal discount rate for costs and effects of 3%. The impact on the cost-effectiveness for patients as young as 6 years old is large as the annual additional costs for Trikafta® of about CHF228 000 per year are included from the start in the economic evaluation. The impact on mortality or lung transplants is only much later in the model; thus, the discount rate impacts these effects. In the meantime, the costs for the chronic Trikafta® treatment have already cumulated over the years, resulting in the presented ICERs.

Figure 31: The impact of applying a discount rate on the net present value of future life years



Source: EUnetHTA guidance document 'Practical considerations when critically assessing economic evaluations'.[125] The net present value (NPV) depends on the applied discount rate. For a life expectancy of 70 years, this NPV equals 70y (0%), 43y (1.5%), 29y (3%) and 19y (5%).

Finally, previous HTA reports have also viewed other CFTR modulators as potential **comparators**. The CADTH analysis also includes a comparison with LUM-IVA in the F/F sub-group and IVA monotherapy in the subgroup of patients with a F/G genotype (see Table 15).[4] The HAS analysis includes LUM-IVA and TEZ-IVA as comparators in the F/F subgroup.[62] However, in both reports, the calculations show that other CFTR modulators can be excluded due to extended dominance, i.e. their cost-effectiveness is worse than the cost-effectiveness of Trikafta® (see results in original HTA reports). Comparing interventions with other relatively expensive interventions that are not cost-effective misrepresents an intervention's cost-effectiveness. In an economic evaluation, excluding other CFTR modulators due to extended dominance is thus justified and comparing Trikafta® with best supportive care is correct.

11. Conclusion

In conclusion, three RCTs compared Trikafta® with standard of care (placebo) in patients aged 6 and older with cystic fibrosis who have one F508del mutation and one minimal function mutation in the CFTR gene (F/MF). In addition, for patients aged 6 and older with cystic fibrosis who are homozygous for F508del mutation (F/F), a network meta-analysis is available comparing Trikafta® with standard of care (placebo). These RCTs and the network meta-analysis provide consistent high-quality evidence for the effectiveness of Trikafta® in comparison with standard of care up to 24 weeks. Beyond 24 weeks, an open-label extension of two RCTs provides non-randomized follow-up data up to 48 weeks, and appears to confirm the effectiveness of Trikafta®. Trikafta® also has been shown to be a safe intervention (with follow-up up to 96 weeks), with most of the reported adverse events being related with the underlying disease (i.e. cystic fibrosis). Adverse events that warrant attention are psychiatric disorders, headache and gastrointestinal symptoms because of frequency, and rash, hepatic adverse events and distal intestinal obstruction syndrome because of severity.

The following evidence gaps were identified: RCTs that compare Trikafta® with standard of care (placebo) in patients aged 6 and older with cystic fibrosis who are homozygous for F508del mutation (F/F), who have one F508del mutation and one residual function mutation in the CFTR gene (F/RF), or who have one F508del mutation and one gating mutation in the CFTR gene (F/G); data on mortality; data on quality of life measured with a generic utility instrument; effectiveness data based on RCTs beyond 24 (- 48) weeks; safety data beyond 96 weeks.

For the economic part, we note that there are a lot of large uncertainties for calculating the cost-effectiveness of Trikafta®. The presence of uncertainty is common in economic evaluations. However, in this case, there is high uncertainty for all key variables: the magnitude of the impact on mortality, the (longer-term) impact on ppFEV1 and the associated impact on quality of life and disease management costs.

To deal with these uncertainties, several scenarios were developed modelling hypothetical mortality hazard ratios. Based on information from previous HTA reports, assumptions were also modelled regarding the impact on the decline in ppFEV1, QoL, disease management costs and lung transplants. Results were also calculated for different time horizons, discount rates for costs and effects and Trikafta® price discounts. Given the high uncertainty for the different input variables, it was not possible to indicate one specific base case analysis. The results for the different scenarios were presented side by side with the intention of displaying the possible ICERs and identifying the most determining variables.

Across all scenarios (excluding two discount rate scenarios), when applying the official list price for Trikafta®, there was no average ICER that was lower than CHF1 million per QALY gained. This result was in line with the results of three of the four identified HTA reports. The main reason is the

annual cost of about CHF228 000 per patient and the chronic use of this intervention. Only when combining a number of 'optimal' scenarios (a mortality hazard ratio of 0.1, an optimistic evolution in ppFEV1 and a lower disease management cost when using Trikafta®) and a price discount of 90%, an ICER of about CHF100 000 per QALY gained was obtained.

Given the large uncertainties regarding several determining variables, future research on the (longer-term) impact of Trikafta® on mortality, ppFEV1, quality of life and disease management costs may shed more light on the cost-effectiveness of this intervention. Notwithstanding, the exploratory scenario analyses performed show that the cost-effectiveness is mainly determined by the annual recurrent cost for Trikafta®.

At the official list price, the total budget impact over 5 years for treating 69 F508del homozygous patients aged 6-11 years would be about CHF78 million. This would become about CHF55 million if substitution costs for Orkambi® and Symdeko® are taken into account. For treating another 70 F508del heterozygous patients aged 6-11 years, the total budget impact over 5 years would be about CHF79 million.

12. References

1. Universitäts Spital Zürich (UZH). Zystische Fibrose. https://www.usz.ch/krankheit/zystische-fibro-se/#:~:text=Die%20zystische%20Fibrose%20ist%20eine,auch%20unter%20Beschwerden%20im%20Verdauungstrakt.
2. Cystische Fibrose Schweiz. Was ist Cystische Fibrose? https://cystischefibroseschweiz.ch/was-ist-cystische-fibrose/.
3. DocCheck Flexikon. Mukoviszidose. https://flexikon.doccheck.com/de/Mukoviszidose.
4. CADTH. Elexacaftor-Tezacaftor-Ivacaftor and Ivacaftor (Trikafta®). CADTH reimbursement review. *Canadian Journal of Health Technologies*. 2022 September 2022;2(9):383.
5. Tice JA, Kuntz KM, Wherry K, Chapman R, Seidner M, Pearson SD, et al. Modulator treatments for cystic fibrosis: effectiveness and value. Evidence report: Institute for Clinical and Economic Review (ICER); 2020.
6. Cystic fibrosis foundation. CFTR Mutation classes. https://www.cff.org/sites/default/files/2021-12/Know-Your-CFTR-Mutations-Infographic.pdf.
7. Swissmedic. Public Summary SwissPAR – Trikafta®. https://www.swissmedic.ch/swissmedic/de/home/ueber-uns/publikationen/public-summary-swiss-par.html#trikafta.
8. Swissmedic. Trikafta®. https://www.swissmedicinfo.ch/ViewMonographie.
9. Bundesamt für Gesundheit (BAG). Spezialitätenliste - Trikafta®. https://www.spezialitaetenliste.ch.
10. Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, et al. ECFS best practice guidelines: the 2018 revision. *J Cyst Fibros*. 2018 Mar;17(2):153-78.
11. Swissmedic. Symdeko®. https://www.swissmedicinfo.ch/ViewMonographie.
12. Swissmedic. Kalydeco®. https://www.swissmedicinfo.ch/ViewMonographie.
13. Swissmedic. Orkambi®. https://www.swissmedicinfo.ch/ViewMonographie.
14. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011 Oct 18;343:d5928.
15. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019 Aug 28;366:l4898.
16. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011 Apr;64(4):401-6.
17. Bailey J, Rozga M, McDonald CM, Bowser EK, Farnham K, Mangus M, et al. Effect of CFTR Modulators on Anthropometric Parameters in Individuals with Cystic Fibrosis: An Evidence Analysis Center Systematic Review. *J Acad Nutr Diet*. 2021 07;121(7):1364-78.e2.
18. Dagenais RVE, Su VCH, Quon BS. Real-world safety of cftr modulators in the treatment of cystic fibrosis: A systematic review. *Journal of Clinical Medicine*. 2021;10(1):1-56.
19. Southern KW, Murphy J, Sinha IP, Nevitt SJ. Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del). *Cochrane Database Syst Rev*. 2020 12 17;12:CD010966.
20. Wang Y, Ma B, Li W, Li P. Efficacy and Safety of Triple Combination Cystic Fibrosis Transmembrane Conductance Regulator Modulators in Patients With Cystic Fibrosis: A Meta-Analysis of Randomized Controlled Trials. *Frontiers in Pharmacology*. 2022;13.
21. CADTH. Elexacaftor-Tezacaftor-Ivacaftor and Ivacaftor (Trikafta®). CADTH reimbursement review. *Canadian Journal of Health Technologies*. 2021 November 2021;1(11):248.
22. GBA. Ivacaftor/Tezacaftor/Elexacaftor (Kaftrio®): Gemeinsamer Bundesausschuss (G-BA); 2022 February 2022.
23. IQWiG. Ivacaftor/Tezacaftor/Elexacaftor und Ivacaftor (zystische Fibrose, 6 bis 11 Jahre, F508del-Mutation, MF-Mutation, heterozygot): Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG); 2022 May 2022.
24. ZIN. GVS-advies elexacaftor/tezacaftor/ivacaftor (Kaftrio) in combinatie met ivacaftor (Kalydeco): Zorginstituut Nederland (ZIN); 2021.
25. ZIN. GVS-advies elexacaftor/tezacaftor/ivacaftor (Kaftrio) in combinatie met ivacaftor (Kalydeco) – uitbreiding nadere voorwaarden: Zorginstituut Nederland (ZIN); 2022.
26. Fajac I, Van BK, Daines C, Durieu I, Goralski J, Heijerman H, et al. Impact of elexacaftor/tezacaftor/ivacaftor triple combination therapy on health-related quality of life in people with

cystic fibrosis heterozygous for F508del and a minimal function mutation: results from a Phase 3 clinical study. Journal of cystic fibrosis; 2020. p. S118-s9.
27. Fajac I, Van BK, Daines C, Durieu I, Goralski J, Heijerman H, et al. Impact of elexacaftor/tezacaftor/ivacaftor triple combination therapy on health-related quality of life in people with cystic fibrosis heterozygous for F508DEL and a minimal function mutation (F/MF): results from a phase 3 clinical study. Thorax; 2021. p. A40-a1.
28. Jain R, Mall M, Drevinek P, Lands L, McKone E, Polineni D, et al. Phase 3 efficacy and safety of the ELX/TEZ/ iva triple combination in people with CF and F508del/minimal function genotypes. Pediatr Pulmonol; 2019. p. 346-7.
29. Keating D, Marigowda G, Burr L, Daines C, Mall MA, McKone EF, et al. VX-445-Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. *N Engl J Med*. 2018 10 25;379(17):1612-20.
30. Mall MA, Brugha R, Gartner S, Legg J, Moeller A, Mondejar-Lopez P, et al. Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Through 11 Years of Age with Cystic Fibrosis Heterozygous for F508del and a Minimal Function Mutation: A Phase 3b, Randomized, Placebo-controlled Study. *Am J Respir Crit Care Med*. 2022 12 01;206(11):1361-9.
31. Middleton PG, Mall MA, Drevinek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *N Engl J Med*. 2019 11 07;381(19):1809-19.
32. Barry PJ, Mall MA, Alvarez A, Colombo C, de Winter-de Groot KM, Fajac I, et al. Triple Therapy for Cystic Fibrosis Phe508del-Gating and -Residual Function Genotypes. *N Engl J Med*. 2021 08 26;385(9):815-25.
33. Heijerman H, McKone E, Downey D, Mall M, Ramsey B, Rowe S, et al. Phase 3 efficacy and safety of the ELX/TEZ/ iva triple combination in people with CF homozygous for the F508del mutation. Pediatr Pulmonol; 2019. p. 347.
34. Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *The Lancet*. 2019;394(10212):1940-8.
35. Sutharsan S, McKone EF, Downey DG, Duckers J, MacGregor G, Tullis E, et al. Efficacy and safety of elexacaftor plus tezacaftor plus ivacaftor versus tezacaftor plus ivacaftor in people with cystic fibrosis homozygous for F508del-CFTR: a 24-week, multicentre, randomised, double-blind, active-controlled, phase 3b trial. *The Lancet Respiratory Medicine*. 2022;10(3):267-77.
36. Bower JK, Volkova N, Ahluwalia N, Sahota G, Xuan F, Chin A, et al. Real-world safety and effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: Interim results of a long-term registry-based study. *Journal of Cystic Fibrosis*. 2023.
37. Burgel PR, Durieu I, Chiron R, Ramel S, Danner-Boucher I, Prevotat A, et al. Rapid improvement after starting elexacaftor-tezacaftor-ivacaftor in patients with cystic fibrosis and advanced pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*. 2021;204(1):64-73.
38. Carnovale V, Iacotucci P, Terlizzi V, Colangelo C, Ferrillo L, Pepe A, et al. Elexacaftor/Tezacaftor/Ivacaftor in Patients with Cystic Fibrosis Homozygous for the F508del Mutation and Advanced Lung Disease: A 48-Week Observational Study. *Journal of Clinical Medicine*. 2022;11(4).
39. Carnovale V, Iacotucci P, Terlizzi V, Colangelo C, Medio P, Ferrillo L, et al. Effectiveness and safety of elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease with the Phe508del/minimal function genotype. *Respir Med*. 2021 Nov-Dec;189:106646.
40. Carrasco Hernández L, Girón Moreno RM, Balaguer Cartagena MN, Peláez A, Sole A, Álvarez Fernández A, et al. Experience With Elexacaftor/Tezacaftor/Ivacaftor in Patients With Cystic Fibrosis and Advanced Disease. *Archivos de Bronconeumologia*. 2023.
41. Griese M, Costa S, Linnemann RW, Mall MA, McKone EF, Polineni D, et al. Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor for 24 Weeks or Longer in People with Cystic Fibrosis and One or More F508del Alleles: Interim Results of an Open-Label Phase 3 Clinical Trial. *Am J Respir Crit Care Med*. 2021 02 01;203(3):381-5.
42. Kos R, Neerincx AH, Fenn DW, Brinkman P, Lub R, Vonk SEM, et al. Real-life efficacy and safety of elexacaftor/tezacaftor/ivacaftor on severe cystic fibrosis lung disease patients. *Pharmacol*. 2022 12;10(6):e01015.
43. Lopes K, Custodio C, Lopes C, Bolas R, Azevedo P. Elexacaftor/tezacaftor/ivacaftor-real-world clinical effectiveness and safety. A single-center Portuguese study. *J Bras Pneumol*. 2023;49(2):e20220312.

44. Martin C, Reynaud-Gaubert M, Hamidfar R, Durieu I, Murris-Espin M, Danner-Boucher I, et al. Sustained effectiveness of elexacaftor-tezacaftor-ivacaftor in lung transplant candidates with cystic fibrosis. *Journal of Cystic Fibrosis*. 2022 05;21(3):489-96.
45. McCoy KS, Blind J, Johnson T, Olson P, Raterman L, Bai S, et al. Clinical change 2 years from start of elexacaftor-tezacaftor-ivacaftor in severe cystic fibrosis. *Pediatr Pulmonol*. 2023 04;58(4):1178-84.
46. O'Shea KM, O'Carroll OM, Carroll C, Grogan B, Connolly A, O'Shaughnessy L, et al. Efficacy of elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease. *Eur Respir J*. 2021 02;57(2):02.
47. Olivier M, Kavvalou A, Welsner M, Hirtz R, Straßburg S, Sutharsan S, et al. Real-life impact of highly effective CFTR modulator therapy in children with cystic fibrosis. *Frontiers in Pharmacology*. 2023;14.
48. Ramos KJ, Guimbellot JS, Valapour M, Bartlett LE, Wai TH, Goss CH, et al. Use of elexacaftor/tezacaftor/ivacaftor among cystic fibrosis lung transplant recipients. *Journal of Cystic Fibrosis*. 2022 09;21(5):745-52.
49. Salomão LZ, Athanazio RA, Rached SZ, Lopes-Pacheco M, Camargo M. A real-life study of elexacaftor-tezacaftor-ivacaftor therapy in people with cystic fibrosis in Brazil. *Pulmonology*. 2023.
50. Salvatore D, Cimino G, Troiani P, Bignamini E, Esposito I, Leonetti G, et al. Elexacaftor/tezacaftor/ivacaftor in children aged 6-11 years with cystic fibrosis, at least one F508DEL allele, and advanced lung disease: A 24-week observational study. *Pediatr Pulmonol*. 2022 09;57(9):2253-6.
51. Stylemans D, Darquenne C, Schuermans D, Verbanck S, Vanderhelst E. Peripheral lung effect of elexacaftor/tezacaftor/ivacaftor in adult cystic fibrosis. *Journal of Cystic Fibrosis*. 2022 01;21(1):160-3.
52. Tewkesbury DH, Athwal V, Bright-Thomas RJ, Jones AM, Barry PJ. Longitudinal effects of elexacaftor/tezacaftor/ivacaftor on liver tests at a large single adult cystic fibrosis centre. *Journal of Cystic Fibrosis*. 2023 03;22(2):256-62.
53. Thomassen JC, Meyer M, Hagmeyer L, Striegel AK, Metz F, Körner R, et al. 6-month approval of Kaftrio® in Germany—First experiences from “real life” of people with CF. *Monatsschrift fur Kinderheilkunde*. 2022.
54. Vanscoy L, Pan A, Mogayzel P, Karnsakul W, Cutting G. 55 Real-world clinical response to Trikafta: The lungs are good, but what about the liver? *Journal of Cystic Fibrosis*. 2021;20:S28.
55. Wainwright C, McColley SA, McNally P, Powers M, Ratjen F, Rayment JH, et al. Long-Term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged 6 Years with Cystic Fibrosis and at Least One F508del Allele: A Phase 3, Open-Label Clinical Trial. *Am J Respir Crit Care Med*. 2023 Jul 01;208(1):68-78.
56. Zemanick ET, Taylor-Cousar JL, Davies J, Gibson RL, Mall MA, McKone EF, et al. A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele. *Am J Respir Crit Care Med*. 2021 06 15;203(12):1522-32.
57. Zhang L, Albon D, Jones M, Bruschwein H. Impact of elexacaftor/tezacaftor/ivacaftor on depression and anxiety in cystic fibrosis. *Therap*. 2022 Jan-Dec;16:17534666221144211.
58. Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *N Engl J Med*. 2017 Nov 23;377(21):2013-23.
59. Tice JA, Kuntz KM, Wherry K, Seidner M, Rind DM, Pearson SD. The effectiveness and value of novel treatments for cystic fibrosis. *J Manag Care Spec Pharm*. 2021 Feb;27(2):276-80.
60. HAS. Kaftrio (elexacaftor/tezacaftor/ivacaftor) en association à l’ivacaftor. Mucoviscidose chez les patients âgés de 12 ans et plus homozygotes pour la mutation F508del ou hétérozygotes et porteurs d'une mutation du gène à fonction minimale. Avis économique: Haute Autorité de Santé (HAS); 2021.
61. Rubin JL, Lopez A, Booth J, Gunther P, Jena AB. Limitations of standard cost-effectiveness methods for health technology assessment of treatments for rare, chronic diseases: a case study of treatment for cystic fibrosis. *J Med Econ*. 2022 Jan-Dec;25(1):783-91.
62. HAS. Kaftrio (elexacaftor/tezacaftor/ivacaftor) en association à l’ivacaftor. Mucoviscidose chez les patients âgés de 6 ans et plus avec au moins une mutation F508del du gène CFTR. Avis économique: Haute Autorité de Santé (HAS); 2022.
63. INESSS. Trikafta – traitement de la fibrose kystique: Institut national d’excellence en santé et en services sociaux (INESSS); 2022.
64. CADTH. Elexacaftor-Tezacaftor-Ivacaftor and Ivacaftor (Trikafta). CADTH reimbursement recommendation. *Canadian Journal of Health Technologies*. 2022;2(7):32.

65. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol*. 2001 Feb 15;153(4):345-52.
66. Arias E, Xu J. United States Life Tables, 2017. *National vital statistics reports*. 2019;68(7).
67. Scotet V, L'Hostis C, Ferec C. The Changing Epidemiology of Cystic Fibrosis: Incidence, Survival and Impact of the CFTR Gene Discovery. *Genes (Basel)*. 2020 May 26;11(6):589.
68. Garrison LP, Jr., Mansley EC, Abbott TA, 3rd, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ISPOR Drug Cost Task Force report--Part II. *Value Health*. 2010 Jan-Feb;13(1):8-13.
69. Moreno SG, Ray JA. The value of innovation under value-based pricing. *J Mark Access Health Policy*. 2016;4.
70. NICE. Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation: Technology appraisal guidance [TA398]: National Institute for Health and Care Excellence (NICE); 2016.
71. CADTH. Lumacaftor/ivacaftor (Orkambi - Vertex Pharmaceuticals (Canada) Incorporated): Canadian Agency for Drugs and Technology in Health (CADTH); 2018.
72. CADTH. CADTH Canadian Drug Expert Commmittee Final Recommendation: Ivacaftor (Kalydeco - Vertex Pharmaceuticals Inc.); Indication: Cystic Fibrosis with R117H Mutation: Canadian Agency for Drugs and Technology in Health (CADTH); 2015.
73. CADTH. CDEC Final Recommendation - Ivacaftor (Kalydeco - Vertex Pharmaceuticals Inc.); Indication: Cystic Fibrosis with G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R mutation: Canadian Agency for Drugs and Technology in Health (CADTH); 2014.
74. CADTH. Final CDEC Recommendation - Ivacaftor (Kalydeco - Vertex Pharmaceuticals (Canada) Incorporated); Indication: Cystic Fibrosis with G551D Mutation: Canadian Agency for Drugs and Technology in Health (CADTH); 2013.
75. Suthoff ED, Bonafede M, Limone B, O'Callaghan L, Sawicki GS, Wagener JS. Healthcare resource utilization associated with ivacaftor use in patients with cystic fibrosis. *J Med Econ*. 2016 Sep;19(9):845-51.
76. Hassan M, Bonafede M, Limone B, Hodgkins P, Suthoff E, Sawicki G. Reduction in pulmonary exacerbations (PEx) after initiation of ivacaftor: a retrospective cohort study among patients with cystic fibrosis (CF) treated in real-world settings. *J Cyst Fibros*. 2016;15:S58.
77. Feng LB, Grosse SD, Green RF, Fink AK, Sawicki GS. Precision Medicine In Action: The Impact Of Ivacaftor On Cystic Fibrosis-Related Hospitalizations. *Health Aff (Millwood)*. 2018 May;37(5):773-9.
78. Vasiliadis HM, Collet JP, Penrod JR, Ferraro P, Poirier C. A cost-effectiveness and cost-utility study of lung transplantation. *J Heart Lung Transplant*. 2005 Sep;24(9):1275-83.
79. Government of Alberta. Alberta Interactive Health Data Application. Average cost of lung transplant procedure in 2017/2018; 2019.
80. Grosse SD, Do TQN, Vu M, Feng LB, Berry JG, Sawicki GS. Healthcare expenditures for privately insured US patients with cystic fibrosis, 2010-2016. *Pediatr Pulmonol*. 2018 Dec;53(12):1611-8.
81. Ministry of Health. Schedule of benefits for physician services under the Health Insurance Act: effective April 1, 2020. Toronto (ON): Ontario; 2020.
82. Neri L, Lucidi V, Catastini P, Colombo C, Group LS. Caregiver burden and vocational participation among parents of adolescents with CF. *Pediatr Pulmonol*. 2016 Mar;51(3):243-52.
83. Milla CE, Ratjen F, Marigowda G, Liu F, Waltz D, Rosenfeld M, et al. Lumacaftor/Ivacaftor in Patients Aged 6-11 Years with Cystic Fibrosis and Homozygous for F508del-CFTR. *Am J Respir Crit Care Med*. 2017 Apr 1;195(7):912-20.
84. Ratjen F, Hug C, Marigowda G, Tian S, Huang X, Stanojevic S, et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. *Lancet Respir Med*. 2017 Jul;5(7):557-67.
85. Walker S, Flume P, McNamara J, Solomon M, Chilvers M, Chmiel J, et al. A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 through 11 years with cystic fibrosis. *J Cyst Fibros*. 2019 Sep;18(5):708-13.
86. Davies JC, Sermet-Gaudelus I, Naehrlich L, Harris RS, Campbell D, Ahluwalia N, et al. A phase 3, double-blind, parallel-group study to evaluate the efficacy and safety of tezacaftor in combination with ivacaftor in participants 6 through 11 years of age with cystic fibrosis homozygous for F508del or heterozygous for the F508del-CFTR mutation and a residual function mutation. *J Cyst Fibros*. 2021 Jan;20(1):68-77.
87. Vertex Pharmaceuticals Incorporated. A Phase 3b, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 6

Through 11 Years of Age Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF). Clinical Study Report (Study VX19-445-116; version 1.0); 2021.
88. Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *Am J Respir Crit Care Med*. 2013 Jun 1;187(11):1219-25.
89. De Boeck K, Munck A, Walker S, Faro A, Hiatt P, Gilmartin G, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *J Cyst Fibros*. 2014 Dec;13(6):674-80.
90. Moss RB, Flume PA, Elborn JS, Cooke J, Rowe SM, McColley SA, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. *Lancet Respir Med*. 2015 Jul;3(7):524-33.
91. Leung GJ, Cho TJ, Kovesi T, Hamid JS, Radhakrishnan D. Variation in lung function and nutritional decline in cystic fibrosis by genotype: An analysis of the Canadian cystic fibrosis registry. *J Cyst Fibros*. 2020 Mar;19(2):255-61.
92. Vertex Pharmaceuticals Incorporated. Pharmacoeconomic evaluation [internal sponsor's report]. In: Drug Reimbursement Review sponsor submission: Trikafta (triple combination therapy [elexacaftor/tezacaftor/ivacaftor & ivacaftor]) tablets, oral 100 mg/50 mg/75 mg and 150 mg. Toronto (ON) (Canada); 2021.
93. Volkova N, Moy K, Evans J, Campbell D, Tian S, Simard C, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries. *J Cyst Fibros*. 2020 Jan;19(1):68-79.
94. Sawicki GS, McKone EF, Pasta DJ, Millar SJ, Wagener JS, Johnson CA, et al. Sustained Benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. *Am J Respir Crit Care Med*. 2015 Oct 1;192(7):836-42.
95. Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *Lancet Respir Med*. 2017 Feb;5(2):107-18.
96. Goss CH, Burns JL. Exacerbations in cystic fibrosis. 1: Epidemiology and pathogenesis. *Thorax*. 2007 Apr;62(4):360-7.
97. Whiting P, Al M, Burgers L, Westwood M, Ryder S, Hoogendoorn M, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. *Health Technol Assess*. 2014 Mar;18(18):1-106.
98. VanDevanter DR, Kahle JS, O'Sullivan AK, Sikirica S, Hodgkins PS. Cystic fibrosis in young children: A review of disease manifestation, progression, and response to early treatment. *J Cyst Fibros*. 2016 Mar;15(2):147-57.
99. Lynch JP, 3rd, Sayah DM, Belperio JA, Weigt SS. Lung transplantation for cystic fibrosis: results, indications, complications, and controversies. *Semin Respir Crit Care Med*. 2015 Apr;36(2):299-320.
100. Stephenson AL, Sykes J, Berthiaume Y, Singer LG, Aaron SD, Whitmore GA, et al. Clinical and demographic factors associated with post-lung transplantation survival in individuals with cystic fibrosis. *J Heart Lung Transplant*. 2015 Sep;34(9):1139-45.
101. Thabut G, Christie JD, Mal H, Fournier M, Brugiere O, Leseche G, et al. Survival benefit of lung transplant for cystic fibrosis since lung allocation score implementation. *Am J Respir Crit Care Med*. 2013 Jun 15;187(12):1335-40.
102. Borowitz D, Lubarsky B, Wilschanski M, Munck A, Gelfond D, Bodewes F, et al. Nutritional Status Improved in Cystic Fibrosis Patients with the G551D Mutation After Treatment with Ivacaftor. *Dig Dis Sci*. 2016 Jan;61(1):198-207.
103. Rosenfeld M, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, et al. An open-label extension study of ivacaftor in children with CF and a CFTR gating mutation initiating treatment at age 2-5 years (KLIMB). *J Cyst Fibros*. 2019 Nov;18(6):838-43.
104. Solem CT, Vera-Llonch M, Tai M, O'Callaghan L. Pulmonary exacerbations, lung dysfunction, and Eq-5d measures in adolescents and adults with cystic fibrosis and homozygous for the F508del-Cftr mutation. *Value Health*. 2016;19(3):A116-A7.
105. Acaster S, Pinder B, Mukuria C, Copans A. Mapping the EQ-5D index from the cystic fibrosis questionnaire-revised using multiple modelling approaches. *Health Qual Life Outcomes*. 2015 Mar 12;13:33.

106. Schechter MS, Trueman D, Farquharson R, Higuchi K, Daines CL. Inhaled aztreonam lysine versus inhaled tobramycin in cystic fibrosis. An economic evaluation. *Ann Am Thorac Soc*. 2015 Jul;12(7):1030-8.
107. Tappenden P, Harnan S, Uttley L, Mildred M, Walshaw M, Taylor C, et al. The cost effectiveness of dry powder antibiotics for the treatment of Pseudomonas aeruginosa in patients with cystic fibrosis. *Pharmacoeconomics*. 2014 Feb;32(2):159-72.
108. INESSS. Trikafta – traitement de la fibrose kystique: Institut national d'excellence en santé et en services sociaux (INESSS); 2021.
109. Busschbach JJ, Horikx PE, van den Bosch JM, Brutel de la Riviere A, de Charro FT. Measuring the quality of life before and after bilateral lung transplantation in patients with cystic fibrosis. *Chest*. 1994 Mar;105(3):911-7.
110. Buzzetti R, Alicandro G, Minicucci L, Notarnicola S, Furnari ML, Giordano G, et al. Validation of a predictive survival model in Italian patients with cystic fibrosis. *J Cyst Fibros*. 2012 Jan;11(1):24-9.
111. Liou TG, Kartsonaki C, Keogh RH, Adler FR. Evaluation of a five-year predicted survival model for cystic fibrosis in later time periods. *Sci Rep*. 2020 Apr 20;10(1):6602.
112. McGarry LJ, Bhaiwala Z, Lopez A, Chandler C, Pelligra CG, Rubin JL, et al. Calibration and validation of modeled 5-year survival predictions among people with cystic fibrosis treated with the cystic fibrosis transmembrane conductance regulator modulator ivacaftor using United States registry data. *PLoS One*. 2023;18(4):e0283479.
113. Hirche TO, Knoop C, Hebestreit H, Shimmin D, Sole A, Elborn JS, et al. Practical guidelines: lung transplantation in patients with cystic fibrosis. *Pulm Med*. 2014;2014:621342.
114. Bleisch B, Schuurmans MM, Klaghofer R, Benden C, Seiler A, Jenewein J. Health-related quality of life and stress-related post-transplant trajectories of lung transplant recipients: a three-year follow-up of the Swiss Transplant Cohort Study. *Swiss Med Wkly*. 2019 Feb 11;149:w20019.
115. Vertex. CF Projected Survival Curves (UK Registry data); 2017.
116. Transplantation Center - University Hospital Zurich. Annual Report; 2021.
117. Transplantation Center - University Hospital Zurich. Annual Report; 2022.
118. Bradley JM, Blume SW, Balp MM, Honeybourne D, Elborn JS. Quality of life and healthcare utilisation in cystic fibrosis: a multicentre study. *Eur Respir J*. 2013 Mar;41(3):571-7.
119. Vertex Pharmaceuticals. Kaftrio - Summary of product characteristics.
120. Ontario Ministry of Health. Schedule of benefits for physician services under the Health Insurance Act: effective April 1, 2020. Toronto; 2020.
121. ZIN. Aantal DDD's per gebruiker 2015-2019 voor ATC-subgroep R05CB13: deoxyribonuclease: Zorginstituut Nederland (ZIN); 2020.
122. Zolin A, Orenti A, Jung A, van Rens J, et al. European Cystic Fibrosis Society Patient Registry (ECFSPR) Annual Report 2021; 2023.
123. EUnetHTA. Guideline: Endpoints used for relative effectiveness assessment - health-related quality of life and utility measures; 2015.
124. Lebecque P, Thimmesch M, Meurrens J, Jeanmart P. Cystic fibrosis: Does it matter to avoid crushing Elexacaftor/Tezacaftor/Ivacaftor (ETI) tablets? *Pediatr Pulmonol*. 2023 Dec;58(12):3603-4.
125. EUnetHTA. Practical considerations when critically assessing economic evaluations. Guidance document.; 2020.
126. Majoor C, Van BK, Daines C, Durieu I, Fajac I, Goralski J, et al. Impact of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) triple combination therapy on health-related quality of life (HRQoL) in people with cystic fibrosis (pwCF) homozygous for F508del (F/F): results from a Phase 3 clinical study. Journal of cystic fibrosis; 2020. p. S32.

13. Appendices

13.1 Search strategies clinical evidence

Table 62: Search strategy clinical evidence – OVID Medline

Search line	Search terms	N hits
#1	exp cystic fibrosis/ or cystic fibrosis.ti,ab.	52054
#2	(deltaF508-CFTR or deltaF508-CFTR protein or f508del).mp.	1461
#3	exp cystic fibrosis transmembrane conductance regulator/ or (cystic fibrosis transmembrane conductance regulator or CFTR).ti,ab.	13241
#4	(cystic fibrosis transmembrane conductance regulator potentiator or CFTR potentiator).ti,ab.	135
#5	(cystic fibrosis transmembrane conductance regulator corrector or CFTR corrector).ti,ab.	105
#6	(cystic fibrosis transmembrane conductance regulator modulator or CFTR modulator).ti,ab.	346
#7	or/1-6	53716
#8	(Elexacaftor or VX 445 or VX-445 or VX445 or Trikafta or Kaftrio).mp.	285
#9	(Ivacaftor or Kalydeco or VX-770 or VX 770 or VX770).ti,ab.	897
#10	(Tezacaftor or Symdeko or VX-661 or VX 661 or VX661).ti,ab.	322
#11	or/8-10	963
#12	7 and 11	936

Table 63: Search strategy clinical evidence – OVID Medline Epub Ahead of Print and Daily Update

Search line	Search terms	N hits
#1	exp cystic fibrosis/ or cystic fibrosis.ti,ab.	483
#2	(deltaF508-CFTR or deltaF508-CFTR protein or f508del).mp.	35
#3	exp cystic fibrosis transmembrane conductance regulator/ or (cystic fibrosis transmembrane conductance regulator or CFTR).ti,ab.	137
#4	(cystic fibrosis transmembrane conductance regulator potentiator or CFTR potentiator).ti,ab.	3
#5	(cystic fibrosis transmembrane conductance regulator corrector or CFTR corrector).ti,ab.	2
#6	(cystic fibrosis transmembrane conductance regulator modulator or CFTR modulator).ti,ab.	33
#7	or/1-6	502
#8	(Elexacaftor or VX 445 or VX-445 or VX445 or Trikafta or Kaftrio).mp.	45
#9	(Ivacaftor or Kalydeco or VX-770 or VX 770 or VX770).ti,ab.	65
#10	(Tezacaftor or Symdeko or VX-661 or VX 661 or VX661).ti,ab.	48
#11	or/8-10	67
#12	7 and 11	67
#13	meta-analysis.mp,pt. or review.pt. or search:.tw.	56663
#14	12 and 13	13

Table 64: Search strategy clinical evidence – Cochrane Library

Search line	Search terms	N hits
#1	MeSH descriptor: [Cystic Fibrosis] explode all trees	2520
#2	cystic fibrosis:ti,ab	6023
#3	("deltaF508-CFTR" or "deltaF508-CFTR protein" or f508del):ti,ab	343
#4	MeSH descriptor: [Cystic Fibrosis Transmembrane Conductance Regulator] explode all trees	122
#5	("cystic fibrosis transmembrane conductance regulator" or CFTR):ti,ab	757
#6	("cystic fibrosis transmembrane conductance regulator potentiator" or CFTR potentiator):ti,ab	116
#7	("cystic fibrosis transmembrane conductance regulator corrector" or CFTR corrector):ti,ab	70
#8	("cystic fibrosis transmembrane conductance regulator modulator" or CFTR modulator):ti,ab	103
#9	32-#8	6329
#10	(Elexacaftor or VX 445 or VX-445 or VX445 or Trikafta or Kaftrio):ti,ab	74
#11	(Ivacaftor or Kalydeco or VX-770 or VX 770 or VX770):ti,ab	506
#12	(Tezacaftor or Symdeko or VX-661 or VX 661 or VX661):ti,ab	171
#13	126-#12	512
#14	#9 and #13	487

Table 65: Search strategy clinical evidence – Embase

Search line	Search terms	N hits
#1	'cystic fibrosis'/exp	86521
#2	'cystic fibrosis':ti,ab	79122
#3	'deltaf508-cftr':ti,ab OR 'deltaf508-cftr protein':ti,ab OR f508del:ti,ab	3900
#4	'cystic fibrosis transmembrane conductance regulator'/exp	18797
#5	'cystic fibrosis transmembrane conductance regulator':ti,ab OR cftr:ti,ab	21532
#6	'cystic fibrosis transmembrane conductance regulator potentiator':ti,ab OR 'cftr potentiator':ti,ab	455
#7	'cystic fibrosis transmembrane conductance regulator corrector':ti,ab OR 'cftr corrector':ti,ab	373
#8	'cystic fibrosis transmembrane conductance regulator modulator':ti,ab OR 'cftr modulator':ti,ab	1335
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	104915
#10	'elexacaftor plus ivacaftor plus tezacaftor'/exp	1168
#11	'elexacaftor'/exp	390
#12	elexacaftor:ti,ab OR 'vx 445':ti,ab OR 'vx-445':ti,ab OR vx445:ti,ab OR trikafta:ti,ab OR kaftrio:ti,ab	1276
#13	ivacaftor:ti,ab OR kalydeco:ti,ab OR 'vx-770':ti,ab OR 'vx 770':ti,ab OR vx770:ti,ab	3552
#14	tezacaftor:ti,ab OR symdeko:ti,ab OR 'vx-661':ti,ab OR 'vx 661':ti,ab OR vx661:ti,ab	1518
#15	'ivacaftor'/exp	3310
#16	'tezacaftor'/exp	658
#17	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	4978
#18	#9 AND #17	4667
#19	#9 AND #17 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [embase]/lim	1723

13.2 Excluded studies based on full-text evaluation

Table 66: Excluded studies based on full-text evaluation

Reference	Reason for exclusion
BAG 2021	No methods of search described
Baroud E, Chaudhary N, Georgiopoulos AM. Management of neuropsychiatric symptoms in adults treated with elexacaftor/tezacaftor/ivacaftor. Pediatr Pulmonol. 2023;58(7):1920-30.	Case series
Breneman A, Soliman YS, Gallitano SM. An acneiform eruption associated with elexacaftor/tezacaftor/ivacaftor treatment. Dermatol Online J. 2021;27(11):15.	Case report
EMA 2020	No methods of search described
EMA 2023	No methods of search described
Fajac I, Daines C, Durieu I, Goralski JL, Heijerman H, Knoop C, et al. Non-respiratory health-related quality of life in people with cystic fibrosis receiving elexacaftor/tezacaftor/ivacaftor. J Cyst Fibros. 2023;22(1):119-23.	Pooled analysis of 2 RCTs (NCT03525444, NCT03525548)
Fila L, Grandcourtova A, Bilkova A, Drevinek P. Elexacaftor-tezacaftor-ivacaftor in patients with cystic fibrosis ineligible for clinical trials: a 24-week observational study. Frontiers in Pharmacology. 2023;14.	No safety data
Ganapathy V, Bailey E, Mortimer K, Lou Y, Yuan J, Mulder K, et al. 56 Real-world clinical effectiveness of elexacaftor/ tezacaftor /ivacaftor and ivacaftor in people with CF: Interim results from the HELIO study. J Cyst Fibros. 2021;20:S28-S9.	Abstract: no RCT, no safety data
Graeber SY, Renz DM, Stahl M, Pallenberg ST, Sommerburg O, Naehrlich L, et al. Effects of Elexacaftor/Tezacaftor/Ivacaftor Therapy on Lung Clearance Index and Magnetic Resonance Imaging in Patients with Cystic Fibrosis and One or Two	No safety data

F508del Alleles. Am J Respir Crit Care Med. 2022;206(3):311-20.	
Graeber SY, Vitzthum C, Pallenberg ST, Naehrlich L, Stahl M, Rohrbach A, et al. Effects of Elexacaftor/Tezacaftor/Ivacaftor Therapy on CFTR Function in Patients with Cystic Fibrosis and One or Two F508del Alleles. Am J Respir Crit Care Med. 2022;205(5):540-9.	No safety data
Gramegna A, Contarini M, Aliberti S, Casciaro R, Blasi F, Castellani C. From Ivacaftor to Triple Combination: A Systematic Review of Efficacy and Safety of CFTR Modulators in People with Cystic Fibrosis. Int. 2020;21(16):16.	No quality appraisal of included studies
Gramegna A, De Petro C, Leonardi G, Contarini M, Amati F, Meazza R, et al. Onset of systemic arterial hypertension after initiation of elexacaftor/tezacaftor/ivacaftor in adults with cystic fibrosis: A case series. J Cyst Fibros. 2022;21(5):885-7.	Case series
Habib AR, Kajbafzadeh M, Desai S, Yang CL, Skolnik K, Quon BS. A Systematic Review of the Clinical Efficacy and Safety of CFTR Modulators in Cystic Fibrosis. Sci. 2019;9(1):7234.	Search done before publications about triple therapy
HAS 2021	No methods of search described
HAS 2022	No methods of search described
Heo S, Young DC, Safirstein J, Bourque B, Antell MH, Diloreto S, et al. Mental status changes during elexacaftor/tezacaftor / ivacaftor therapy. J Cyst Fibros. 2022;21(2):339-43.	Case series
Hong E, Shi A, Beringer P. Drug-drug interactions involving CFTR modulators: a review of the evidence and clinical implications. Expert Opin Drug Metab Toxicol. 2023;19(4):203-16.	Narrative review
Hu MK, Wood G, Dempsey O. 'Triple therapy' (elexacaftor, tezacaftor, ivacaftor) skin rash in patients with cystic fibrosis. Postgrad Med J. 2022;98(1156):86.	Case report
Ibrahim H, Danish H, Morrissey D, Deasy KF, McCarthy M, Dorgan J, et al. Individualized approach to elexacaftor/tezacaftor/ivacaftor dosing in cystic fibrosis, in response to self-	Case series

reported anxiety and neurocognitive adverse events: A case series. Frontiers in Pharmacology. 2023;14.	
INESSS 2022	No methods of search described
Jordan KD, Zemanick ET, Taylor-Cousar JL, Hoppe JE. Managing cystic fibrosis in children aged 6-11yrs: a critical review of elexacaftor/tezacaftor/ivacaftor combination therapy. Expert Rev Respir Med. 2023;17(2):97-108.	Narrative review
Kapouni N, Moustaki M, Douros K, Loukou I. Efficacy and Safety of Elexacaftor-Tezacaftor-Ivacaftor in the Treatment of Cystic Fibrosis: A Systematic Review. Children. 2023;10(3).	No quality appraisal of included studies
Livnat G, Dagan A, Heching M, Shmueli E, Prais D, Yaacoby-Bianu K, et al. Treatment effects of Elexacaftor/Tezacaftor/Ivacaftor in people with CF carrying non-F508del mutations. J Cyst Fibros. 2023;22(3):450-5.	Non-F508del mutations
Lowry S, Mogayzel PJ, Oshima K, Karnsakul W. Drug-induced liver injury from elexacaftor/ivacaftor/tezacaftor. J Cyst Fibros. 2022;21(2):e99-e101.	Case report
Majoor C, Van BK, Daines C, Durieu I, Fajac I, Goralski J, et al. Impact of elexacaftor/tezacaftor/ ivacaftor triple combination therapy on health-related quality of life in people with cystic fibrosis homozygous for F508del: results from a phase 3 clinical study. Pediatr Pulmonol [Internet]. 2020; 55(Suppl 2):[225 p.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02243954/full.	Abstract: RCT with active control (NCT03525548), no safety data
Majoor C, Van BK, Daines C, Durieu I, Fajac I, Goralski J, et al. Impact of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) triple combination therapy on health-related quality of life (HRQoL) in people with cystic fibrosis (pwCF) homozygous for F508del (F/F): results from a Phase 3 clinical study. J Cyst Fibros [Internet]. 2020; 19:[S32 p.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02243953/full.	Abstract: RCT with active control (NCT03525548), no safety data
Majoor C, Van BK, Daines C, Durieu I, Fajac I, Goralski J, et al. Impact of elexacaftor/tezacaftor/ivacaftor triple combination therapy on health-related quality of life in people with cystic	Abstract: RCT with active control (NCT03525548), no safety data

fibrosis homozygous for F508DEL (F/F): results from a phase 3 clinical study. Thorax [Internet]. 2021; 76(Suppl 1):[A41-a2 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02261225/full	
Marshall LZ, Espinosa R, Starner CI, Gleason PP. Real-world outcomes and direct care cost before and after elexacaftor/tezacaftor/ivacaftor initiation in commercially insured members with cystic fibrosis. J Manag Care Spec Pharm. 2023;29(6):599-606.	No safety data
Nichols D, Paynter A, Kirby S, VanDalfsen J, Khan U, Heltshe S, et al. Clinical effectiveness of elexacaftor/ tezacaftor/ivacaftor: the longitudinal promise study. Pediatr Pulmonol [Internet]. 2020; 55(Suppl 2):[210-1 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02244169/full.	No safety data
Nichols DP, Paynter AC, Heltshe SL, Donaldson SH, Frederick CA, Freedman SD, et al. Clinical Effectiveness of Elexacaftor/Tezacaftor/Ivacaftor in People with Cystic Fibrosis: A Clinical Trial. Am J Respir Crit Care Med. 2022;205(5):529-39.	No safety data
Nieto Royo R, Durán Barata D, Barrios Barreto D, Briceño Franquiz W, Máiz Carro L. Safety and effectiveness of treatment with elexacaftor, tezacaftor and ivacaftor in adults with cystic fibrosis. Med Clin (Barc). 2023.	Spanish
NIHR 2019	No methods of search described
Okroglic L, Sohier P, Martin C, Lheure C, Franck N, Honore I, et al. Acneiform Eruption Following Elexacaftor-Tezacaftor-Ivacaftor Treatment in Patients With Cystic Fibrosis. JAMA Dermatol. 2023;159(1):68-72.	Case series
Piehler L, Thalemann R, Lehmann C, Thee S, Röhmel J, Syunyaeva Z, et al. Effects of elexacaftor/tezacaftor/ivacaftor therapy on mental health of patients with cystic fibrosis. Frontiers in Pharmacology. 2023;14.	No safety data
Purkayastha D, Agtarap K, Wong K, Pereira O, Co J, Pakhale S, et al. Drug-drug interactions with CFTR modulator therapy in	No quality appraisal of included studies

cystic fibrosis: Focus on Trikafta®/Kaftrio®. J Cyst Fibros. 2023;22(3):478-83.	
Ragan H, Autry E, Bomersback T, Hewlett J, Kormelink L, Safirstein J, et al. The use of elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis postliver transplant: A case series. Pediatr Pulmonol. 2022;57(2):411-7.	Case series
Rotolo SM, Duehlmeyer S, Slack SM, Jacobs HR, Heckman B. Testicular pain following initiation of elexacaftor/tezacaftor/ivacaftor in males with cystic fibrosis. J Cyst Fibros. 2020;19(5):e39-e41.	Case series
Schembri L, Warraich S, Bentley S, Carr SB, Balfour-Lynn IM. Impact of elexacaftor/tezacaftor/ivacaftor on fat-soluble vitamin levels in children with cystic fibrosis. J Cyst Fibros. 2023.	No safety data
Schnell A, Jungert J, Klett D, Hober H, Kaiser N, Ruppel R, et al. Increase of liver stiffness and altered bile acid metabolism after triple CFTR modulator initiation in children and young adults with cystic fibrosis. Liver Int. 2023;43(4):878-87.	No safety data
Schwarzenberg SJ, Vu PT, Skalland M, Hoffman LR, Pope C, Gelfond D, et al. Elexacaftor/tezacaftor/ivacaftor and gastrointestinal outcomes in cystic fibrosis: Report of promise-GI. J Cyst Fibros. 2023;22(2):282-9.	No safety data
Southern KW, Barben J, Goldring S, Kneen R, Southward S, Rajeev Y, et al. Raised Intracranial Pressure in Three Children with Cystic Fibrosis Receiving Elexacaftor-Tezacaftor-Ivacaftor Modulator Therapy. Am J Respir Crit Care Med. 2023;208(1):103-5.	Case report
Southern KW, Murphy J, Sinha IP, Nevitt SJ. A systematic cochrane review of corrector therapies (with or without potentiators) for people with cystic fibrosis with class II gene variants (most commonly F508DEL) [1]. Paediatr Respir Rev. 2021;38:33-6.	Summary of Cochrane review
Southern KW, Patel S, Sinha IP, Nevitt SJ. A systematic Cochrane Review of correctors (specific therapies for class II CFTR mutations) for cystic fibrosis [1]. Paediatr Respir Rev. 2019;30:25-6.	Summary of Cochrane review

Streibel C, Willers CC, Pusterla O, Bauman G, Stranzinger E, Brabandt B, et al. Effects of elexacaftor/tezacaftor/ivacaftor therapy in children with cystic fibrosis – a comprehensive assessment using lung clearance index, spirometry, and functional and structural lung MRI. J Cyst Fibros. 2023.	No safety data
Tachtatzis P, Spoletini G, Clifton I, Etherington C, Peckham D. Changes in liver biochemistry and tacrolimus levels following the introduction of elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis and liver transplant. J Cyst Fibros. 2023.	Case series
Taylor-Cousar JL, Mall MA, Ramsey BW, McKone EF, Tullis E, Marigowda G, et al. Clinical development of triple-combination CFTR modulators for cystic fibrosis patients with one or two F508del alleles. ERJ Open Research. 2019;5(2).	No methods of search described
Tümmler B. Post-approval studies with the CFTR modulators Elexacaftor-Tezacaftor—Ivacaftor. Frontiers in Pharmacology. 2023;14.	No systematic search
Yousif Hamdan AH, Zakaria F, Lourdes Pormento MK, Lawal OS, Opiegbe A, Zahid S, et al. Cystic Fibrosis Transmembrane Conductance Regulator Protein Modulators in Children and Adolescents with different CF Genotypes - Systematic Review and Meta-Analysis. Curr Rev Clin Exp Pharmacol. 2023;01:01.	No full-text

13.3 GRADE tables

Table 67: Trikafta® (ELX 50 mg / TEZ 100 mg / IVA 150 mg) compared to standard care / placebo for patients with cystic fibrosis aged 18+ and with genotype F/MF

N studies	Study design	Certainty assessment					N patients		Effect estimate (95%CI)	Certainty
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other bias	Trikafta® (ELX 50 mg / TEZ 100 mg / IVA 150 mg)	Standard care / placebo		
Percentage of predicted FEV1 at day 29										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	10	12	MD 11.1 higher (5.42 higher to 16.78 higher)	⊕⊕⊕⊕ High
CFQ-R respiratory domain score at day 29										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	10	12	MD 17.2 points higher (4.44 higher to 29.96 higher)	⊕⊕⊕⊕ High
Sweat chloride at day 29										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	10	12	MD 36 mmol/l lower (47.23 lower to 24.77 lower)	⊕⊕⊕⊕ High

CI: confidence interval; MD: mean difference; [a] Optimal information size reached (power calculation using online tool: https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html).

Table 68: Trikafta® (ELX 100 mg / TEZ 100 mg / IVA 150 mg) compared to standard care / placebo for patients with cystic fibrosis aged 18+ and with genotype F/MF

N studies	Study design	Certainty assessment					N patients		Effect estimate (95%CI)	Certainty
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other bias	Trikafta® (ELX 100 mg / TEZ 100 mg / IVA 150 mg)	Standard care / placebo		
Percentage of predicted FEV1 at day 29										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	22	12	MD 7.9 higher (3.12 higher to 12.68 higher)	⊕⊕⊕⊕ High
CFQ-R respiratory domain score at day 29										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	22	12	MD 14.5 points higher (3.72 higher to 25.28 higher)	⊕⊕⊕⊕ High
Sweat chloride at day 29										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	22	12	MD 31 mmol/l lower (40.41 lower to 21.59 lower)	⊕⊕⊕⊕ High

CI: confidence interval; MD: mean difference; [a] Optimal information size reached (power calculation using online tool: https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html).

Table 69: Trikafta® (ELX 200 mg / TEZ 100 mg / IVA 150 mg) compared to standard care / placebo for patients with cystic fibrosis aged 18+ and with genotype F/MF

N studies	Study design	Certainty assessment					N patients		Effect estimate (95%CI)	Certainty
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other bias	Trikafta® (ELX 200 mg / TEZ 100 mg / IVA 150 mg)	Standard care / placebo		
Percentage of predicted FEV1 up to 1 month										
2	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	165	155	MD 13.62 higher (12.02 higher to 15.22 higher)	⊕⊕⊕⊕ High
CFQ-R respiratory domain score at day 29										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	21	12	MD 21.3 higher (10.53 higher to 32.07 higher)	⊕⊕⊕⊕ High
Sweat chloride at day 29										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	21	12	MD 36.9 mmol/l lower (46.43 lower to 27.37 lower)	⊕⊕⊕⊕ High

CI: confidence interval; MD: mean difference; [a] Optimal information size reached (power calculation using online tool: https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html).

Table 70: Trikafta® (ELX 200 mg / TEZ 100 mg / IVA 150 mg) compared to standard care / placebo for patients with cystic fibrosis aged 12+ and with genotype F/MF

N studies	Study design	Certainty assessment					N patients		Effect estimate (95%CI)	Certainty
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other bias	Trikafta® (ELX 200 mg / TEZ 100 mg / IVA 150 mg)	Standard care / placebo		
Percentage of predicted FEV1 up to 1 month										
2	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	221	215	MD 13.8 higher (12.27 higher to 15.33 higher)	⊕⊕⊕⊕ High
Percentage of predicted FEV1 at 24 weeks										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	200	203	MD 14.3 higher (12.7 higher to 15.8 higher)	⊕⊕⊕⊕ High
Pulmonary exacerbations at 24 weeks										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	41/200	113/203	Rate ratio 0.37 (0.25 to 0.55)	⊕⊕⊕⊕ High
BMI at 24 weeks										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	200	203	MD 1.04 higher (0.85 higher to 1.23 higher)	⊕⊕⊕⊕ High

N studies	Study design	Certainty assessment					N patients		Effect estimate (95%CI)	Certainty
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other bias	Trikafta® (ELX 200 mg / TEZ 100 mg / IVA 150 mg)	Standard care / placebo		
CFQ-R respiratory domain score up to 1 month										
2	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	221	215	MD 20.1 points higher (17.07 higher to 23.14 higher)	⊕⊕⊕⊕ High
CFQ-R respiratory domain score at 24 weeks										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	200	203	MD 20.2 points higher (17.5 higher to 23 higher)	⊕⊕⊕⊕ High
Sweat chloride up to 1 month										
2	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	221	215	MD 40.96 mmol/l lower (43.6 lower to 38.33 lower)	⊕⊕⊕⊕ High
Sweat chloride at 24 weeks										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	200	203	MD 41.8 mmol/l lower (44.4 lower to 39.3 lower)	⊕⊕⊕⊕ High

CI: confidence interval; MD: mean difference; [a] Optimal information size reached (power calculation using online tool: https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html).

Table 71: Trikafta® (ELX 200 mg / TEZ 100 mg / IVA 150 mg) compared to standard care / placebo for patients with cystic fibrosis aged 12-18y and with genotype F/MF

N studies	Study design	Certainty assessment					N patients		Effect estimate (95%CI)	Certainty
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other bias	Trikafta® (ELX 200 mg / TEZ 100 mg / IVA 150 mg)	Standard care / placebo		
Percentage of predicted FEV1 at 4 weeks										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	56	60	MD 13.8 higher (10 higher to 17.5 higher)	⊕⊕⊕⊕ High

CI: confidence interval; MD: mean difference; [a] Optimal information size reached (power calculation using online tool: https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html).

Table 72: Trikafta® (ELX 100-200 mg / TEZ 50-100 mg / IVA 75-150 mg) compared to standard care / placebo for patients with cystic fibrosis aged 6-11y and with genotype F/MF

N studies	Study design	Certainty assessment					N patients		Effect estimate (95%CI)	Certainty
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other bias	Trikafta® (ELX 100-200 mg / TEZ 100 mg / IVA 150 mg)	Standard care / placebo		
Percentage of predicted FEV1 at 24 weeks										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	60	61	MD 11 higher (6.9 higher to 15.1 higher)	⊕⊕⊕⊕ High

N studies	Study design	Certainty assessment					N patients		Effect estimate (95%CI)	Certainty
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other bias	Trikafta® (ELX 100-200 mg / TEZ 100 mg / IVA 150 mg)	Standard care / placebo		
CFQ-R respiratory domain score at 24 weeks										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	60	61	MD 5.5 points higher (1.1 higher to 10 higher)	⊕⊕⊕⊕ High
Lung clearance index 2.5 at 24 weeks										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	60	61	MD 2.26 lower (2.71 lower to 1.81 lower)	⊕⊕⊕⊕ High
Sweat chloride at 24 weeks										
1	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	60	61	MD 51.2 mmol/l lower (55.3 lower to 47.1 lower)	⊕⊕⊕⊕ High

CI: confidence interval; MD: mean difference; [a] Optimal information size reached (power calculation using online tool: https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html).

Table 73: Trikafta® (ELX 200 mg / TEZ 100 mg / IVA 150 mg) compared to standard care / placebo for patients with cystic fibrosis aged 12+ and with genotype F/F

N studies	Study design	Certainty assessment					N patients		Effect estimate (95%CI)	Certainty
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other bias	Trikafta® (ELX 100-200 mg / TEZ 100 mg / IVA 150 mg)	Standard care / placebo		
Percentage of predicted FEV1 at 24 weeks										
2	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	55	256	MD 14 higher (11.3 higher to 16.7 higher)	⊕⊕⊕⊕ High
CFQ-R respiratory domain score at 24 weeks										
2	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	55	256	MD 22.5 points higher (16.6 higher to 28.4 higher)	⊕⊕⊕⊕ High
Sweat chloride at 24 weeks										
2	RCT	Not serious	Not serious	Not serious	Not serious[a]	None	55	256	MD 55.2 mmol/l lower (60.4 lower to 50 lower)	⊕⊕⊕⊕ High

CI: confidence interval; MD: mean difference; [a] Optimal information size reached (power calculation using online tool: https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html).

13.4 Search strategy economic evaluations

INAHTA HTA database

On July 30, 2023, the HTA database of the International Network of Agencies for Health Technology Assessment (INAHTA) was searched (https://www.inahta.org/hta-database/). The following terms were used to perform a sensitive search in this HTA database: ‘kaftrio’ (1 hit); ‘trikafta’ (1 hit); ivacaftor (59 hits); tezacaftor (34 hits); elexacaftor (21 hits); and CFTR modulator (0 hits). Combining these terms provided 59 references.

Websites HTA institutes

During the first week of August, 2023, the websites of HTA institutes that are INAHTA members were searched using the terms ‘kaftrio’, ‘trikafta’, ‘ivacaftor’ or ‘CFTR modulator’. To search within a single website, the Google site-search function was used. Table 74 gives an overview of the INAHTA members.

Table 74: List of INAHTA members

Abbreviation	Institute	Country
ACE	Agency for Care Effectiveness	Singapore
AETS	Agencia de Evaluación de Tecnologias Sanitarias	Spain
AETSA	Andalusian Agency for Health Technology Assessment	Spain
AGENAS	The Agency for Regional Healthcare	Italy
AHRQ	Agency for Healthcare Research and Quality	USA
AHTA	Adelaide Health Technology Assessment	Australia
AIHTA	Austrian Institute for Health Technology Assessment	Austria
ANS	Agência Nacional de Saúde Suplementar / National Regulatory Agency for Private Health Insurance and Plans	Brazil
AOTMIT	Agency for Health Technology Assessment and Tariff System	Poland
AP-HP	Assistance Publique – Hôpitaux de Paris	France
AQuAS	Agència de Qualitat i Avaluació Sanitàries de Catalunya	Spain
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	Australia

AVALIA-T	Galician Agency for Health Technology Assessment	Spain
C2H	Center for Outcomes Research and Economic Evaluation for Health	Japan
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada
CA-HTA	Central Administration of Health Technology Assessment	Egypt
CDE	Center for Drug Evaluation	Taiwan
CONITEC	National Committee for Technology Incorporation	Brazil
DEFACTUM	Social & Health Services and Labour Market	Denmark
DIGEMID	General Directorate of Medicines, Supplies and Drugs	Peru
FinCCHTA	Finnish Coordinating Center for Health Technology Assessment	Finland
G-BA	The German Health Care System and the Federal Joint Committee	Germany
GOEG	Gesundheit Österreich	Austria
HAD-Uruguay	Health Assessment Division, Ministry of Public Health	Uruguay
HAS	Haute Autorité de Santé	France
HIQA	Health Information and Quality Authority	Ireland
HIS	Healthcare Improvement Scotland	United Kingdom
HTW	Health Technology Wales	United Kingdom
IACS	Health Sciences Institute in Aragon	Spain
IECS	Institute for Clinical Effectiveness and Health Policy	Argentina
IETS	Instituto de Evaluación Tecnológica en Salud	Colombia
IETSI	Institute of Health Technology Assessment and Research	Peru
IHE	Institute of Health Economics	Canada
INEAS	National Authority for Assessment and Accreditation in Healthcare	Tunisia

INESSS	Institut national d'excellence en santé et en services sociaux	Canada
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE	Belgian Federal Health Care Knowledge Centre	Belgium
MaHTAS	Health Technology Assessment Section at Ministry of Health of Malaysia	Malaysia
NECA	National Evidence-based healthcare Collaboration Agency	Korea
NICE	National Institute for Health and Care Excellence	United Kingdom
NIHO	National institute for Value and Technologies in Healthcare	Slovak Republic
NIHR	National Institute for Health Research	United Kingdom
NIPH	Norwegian Institute of Public Health	Norway
OH	Ontario Health	Canada
OSTEBA	Basque Office for Health Technology Assessment	Spain
RER	Regione Emilia-Romagna	Italy
SK-NRCHD	Salidat Kairbekova National Research Center for Health Development	Kazakhstan
SBU	Swedish Council on Technology Assessment in Health Care	Sweden
SEC	Department of HTA at the State Expert Centre of the Ministry of Health	Ukraine
SFOPH	Swiss Federal Office of Public Health	Switzerland
UVT	HTA Unit in A. Gemelli University Hospital	Italy
ZIN	Zorginstituut Nederland	The Netherlands
ZonMw	The Medical and Health Research Council of The Netherlands	The Netherlands

CEA registry

On September 27, 2023, the Cost-Effectiveness Analysis (CEA) Registry was searched using the terms ‘trikafta’ or ‘kaftrio’ (cear.tuftsmedicalcenter.org). No references were identified.

Medline

On September 29, 2023, Medline (OVID and Pubmed) was searched. In OVID, no search terms were suggested when using the terms ‘kaftrio’ or ‘trikafta’. In contrast, in Pubmed, the term ‘elexacaftor, ivacaftor, tezacaftor drug combination [Supplementary Concept]’ was suggested. Therefore, it was chosen to continue the search on Pubmed. Given the low number of hits linked to the search terms for the intervention (see Table 75) it was decided not to add the search filter for economic studies from SIGN (https://www.sign.ac.uk/what-we-do/methodology/search-filters/).

Table 75: Search strategy economic evaluations – Medline (Pubmed)

Date	September 29, 2023		
Date covered	All		
Search strategy	1	"elexacaftor, ivacaftor, tezacaftor drug combination" [Supplementary Concept]	37
	2	Trikafta	98
	3	Kaftrio	19
	4	#1 or #2 or #3	**108 references**

Embase

On September 29, 2023, Embase was searched. The search filter for economic studies from SIGN was used (https://www.sign.ac.uk/what-we-do/methodology/search-filters/) in combination with the suggested Emtree term for ‘trikafta’ and ‘kaftrio’ (Table 76). This resulted in 288 identified references.

Table 76: Search strategy economic evaluations – EMBASE

Date	September 29, 2023		
Date covered	All		
Search strategy	1	socioeconomics'/exp	449444
	2	cost benefit analysis'/exp	88847
	3	cost effectiveness analysis'/exp	164400

	4	cost of illness'/exp	20255
	5	cost control'/exp	72042
	6	economic aspect'/exp	1899819
	7	financial management'/exp	496291
	8	health care cost'/exp	313545
	9	health care financing'/exp	13578
	10	health economics'/exp	958313
	11	hospital cost'/exp	41918
	12	finance'/exp OR 'funding'/exp OR fiscal OR financial	322035
	13	cost minimization analysis'/exp	3718
	14	cost*:de,cl,ab,ti	1204758
	15	estimate*:de,cl,ab,ti	1380846
	16	variable*:de,cl,ab,ti	1273890
	17	unit:de,cl,ab,ti	774693
	18	#14' NEAR/1 '#15' OR '#15' NEAR/1 '#14'	28630
	19	#14' NEAR/1 '#16' OR '#16' NEAR/1 '#14'	34705
	20	#14' NEAR/1 '#17' OR '#17' NEAR/1 '#14'	19709
	21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #18 OR #19 OR #20	6434952
	22	'elexacaftor plus ivacaftor plus te-zacaftor'/exp	1232
	23	#21 AND #22	**288 references**
Remark:	Embase suggests to use the search term 'elexacaftor plus ivacaftor plus tezacaftor' when entering the search terms ‘trikafta’ or ‘kaftrio’.		

From the 396 references in Medline (Pubmed) and Embase, 17 duplicates were removed, resulting in 379 references.

13.5 Data extraction sheet for economic evaluations

Table 77: Data extraction sheet

	Elements to be extracted from the original economic evaluation
1	Reference (including all authors)
2	Conflict of interest and/or study funding
3	Country
4	Study question
5	Type of analysis (analytic technique) – e.g. cost-effectiveness analysis, cost-utility analysis, etc.
6	Design – e.g. Markov model, decision tree, etc.
7	Population
8	Intervention
9	Comparator
10	Time horizon
11	Discount rate for costs and/or effects
12	Perspective
13	Costs Cost items included; Measurement of resource use; Valuation of resource use; Data sources; Currency and cost year; Other aspects
14	Outcomes Endpoints taken into account and/or health states; Valuation of health states; Treatment effect and Extrapolation; Utility assessment (Quality of Life); Data sources for outcomes; Other aspects
15	Uncertainty – Scenario analysis; Sensitivity analysis
16	Assumptions
17	Results Cost-effectiveness and/or cost-utility (base case); Scenario analysis; Sensitivity analysis; Other aspects
18	Conclusions The conclusion of the authors (which can be discussed in the actual critical appraisal)
19	Remarks – e.g. limitations of the study