Single Technology assessment

Tezacaftor/ivacaftor (Symkevi) in combination with ivacaftor (Kalydeco) for the treatment of patients ≥12 years with cystic fibrosis

ID2018_112

07-02-2020

Norwegian Medicines Agency

PREFACE

The implementation of The National System for Managed Introduction of New Health Technologies within the Specialist Health Service will help to ensure that assessment of appropriate new technologies is conducted in a systematic manner with respect to efficacy and safety, as well as its impact on health and society.

The main aim of the new system is described in the National Health and Care Plan 2011-2015 and the White Paper 10 - Good Quality - Safe Services (2012-2013). As outlined, the Regional Health Authorities, the Norwegian Knowledge Centre for Health Services, the Norwegian Medicines Agency and the Directorate of Health will collaborate on tasks related to the establishment and implementation of the new system. Eventually, The National System for Managed Introduction of New Health Technologies within the Specialist Health Service will assist in the rational use of health care resources.

The Norwegian Medicines Agency (NoMA) has been assigned responsibility for evaluating Single Technology Assessments (STA) of individual pharmaceuticals. A Single Technology Assessment is a systematic summary of evidence, based on research on efficacy, safety and impact assessment. For pharmaceuticals, this will usually revolve around budgetary consequences or resource allocation. The burden of proof relating to the documentation of efficacy, safety and cost-effectiveness is borne by the MA-holder for the pharmaceutical under review. NoMA can provide guidance to pharmaceutical companies should the need arise.

Once the relevant evidence has been submitted, NoMA will make an assessment of all important clinical outcomes, use of resources, as well as any assumptions made in the analysis and results presented by the MA holder. NoMA does not perform its own health economic analyses. NoMA may request additional information from the pharmaceutical company, as well as perform additional calculations of the costs and cost-effectiveness using the submitted model, if necessary.

NoMA will also evaluate the relative efficacy and incremental costs in relation to a relevant comparator. The cost-effectiveness ratio will be weighed against the severity of the relevant condition/disease. NoMA will not, however, assess the benefit-risk balance already assessed under the market authorisation procedure. Further information provided by EMA can be found in SmPC.

Single Technology Assessment of pharmaceuticals is intended to support sound decision-making of potential introductions of new technologies, and prioritisation of this at the Health Authority level. NoMA has no decision-making authority in this system.

All completed assessments will be published and available to the public (www.legemiddelverket.no).

EXECUTIVE SUMMARY

Rationale

Single technology assessment (STA) of tezacaftor/ivacaftor (TEZ/IVA, Symkevi) in combination with ivacaftor (IVA, Kalydeco) for the treatment of patients ≥12 years with Cystic Fibrosis (CF). The benefits and risks of TEZ/IVA have been documented through the approval of marketing authorisation. In this STA, NoMA has assessed treatment with TEZ/IVA against the prioritisation criteria – the benefit criterion, the resource criterion and the severity criterion, according to the Summary of Product Characteristics (SmPC) for TEZ/IVA, and the requested specifications from the Ordering Forum (request number ID2018_112, https://nyemetoder.no/metoder/tezakaftorivakaftor-). NoMA´s assessment is based mainly, but not exclusively, on the documentation presented by Vertex.

Background

CF is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality, and at present, there is no cure. CF is caused by mutations in the CFTR gene that result in the absent or deficient function of the CFTR (Cystic Fibrosis Transmembrane conductance Regulator) protein at the cell surface. The CFTR protein is an epithelial chloride channel responsible for regulating salt and water absorption and secretion. The failure to regulate chloride transport in organs results in the multisystem pathology associated with CF. Multiple mutations exists; some genotypes are considered mild, whilst others are considered severe on a group level. Patients with a double copy of F508del (i.e. homozygotes (F/F)) constitute about 40% of European CF patients. On a group level, patients with F/F mutations are considered to have a severe illness with poor or lacking CFTR function. Patients with one copy of F508del and another mutation coding for residual function (F/RF) are considered to have a better CFTR function than F/F patients. TEZ/IVA is a CFTR modulator treatment for CF patients with F/F mutation, and 14 specific F/RF mutations. This STA evaluates the cost-effectiveness of TEZ/IVA for both populations; the F/F and F/RF subgroups.

Patient population

The current patient population in Norway is approximately 110 patients with the F/F mutational status, and 30 patients with F/RF mutations as per label. They are expected to be candidates for continuous treatment with TEZ/IVA. Patient numbers are expected to be stable.

Severity and shortfall

The current prognosis for patients with CF is poor. In Norway, the degree of severity affects whether the costs are considered reasonable relative to the benefit of the treatment. NoMA has estimated that patients ≥12 years with CF have an absolute shortfall of approximately 30 and 28 Quality Adjusted Life Years (QALYs) for respectively the F/F and F/RF subpopulations.

Treatment in a Norwegian setting

Norway follows European CF-guidelines, and there are also developed national recommendations (1-3). With best supportive care (BSC) the primary goal is to slow down the progression/loss of lung function, maintain nutritional status, and manage co-morbidities. The CFTR modulators IVA monotherapy and

lumacaftor/ivacaftor (LUM/IVA, Orkambi) are used in Norwegian clinical practice for patients with certain genotypes. At present no CFTR modulators are available in Norway for treating CF patients with F/RF genotype, and BSC is considered to be the relevant comparator for this population. LUM/IVA is authorised for the treatment of patients with F/F genotype and 30 Norwegian patients are receiving treatment with this drug. However, cost-effectiveness for LUM/IVA has never been established. Therefore, NoMA considers BSC to be a relevant comparator for the F/F population. NoMA has included an evaluation of a comparison with LUM/IVA supplementary to the main analysis.

Clinical efficacy

The clinical efficacy and safety of TEZ/IVA was demonstrated in two phase 3 randomised controlled trials:

- F/F population: the 24 week EVOLVE study (N = 510)
- F/RF population: the 8 (+8) week crossover study EXPAND (N = 248)

TEZ/IVA plus BSC is compared to placebo plus BSC in these trials. Patients from EVOLVE and EXPAND entered the open, one-armed follow-up trial referred to as Study 110. All patients received TEZ/IVA in Study 110. All studies have now been completed. Final cut off data from follow-up Study 110 was received on 22nd of October 2019.

The EVOLVE and EXPAND studies showed statistically significant changes in lung function (i.e. the primary endpoint ppFEV1) in favour of TEZ/IVA compared to BSC alone. Follow-up data from Study 110 shows that improvement in lung function is maintained for additional 96 weeks for patients with F/RF mutation. For patients with F/F mutation lung function improved compared to baseline. However, Study 110 lacks a comparator (BSC) arm and hence does not provide further information about the relative effect.

A statistical significant improvement in rate for pulmonary exacerbations (PEx) was shown in favour of TEZ/IVA in the EVOLVE trial (F/F population). PEx was an explorative endpoint in the EXPAND trial (F/RF population) and hence results from this trial are descriptive only. A positive trend for improvement in PEx rate was shown for TEZ/IVA. After 96 additional weeks of treatment in Study 110 the trend was positive for PEx rate in both F/F and F/RF populations.

The TEZ/IVA trials are considered relevant for Norwegian clinical practice.

Efficacy in children under 12 years has not been assessed by EMA.

Safety

The most common adverse reactions experienced by patients receiving TEZ/IVA versus placebo in the pooled, placebo-controlled, phase 3 studies were headache (14% versus 12% for placebo) and nasopharyngitis (12% versus 10% for placebo).

Safety in children under 12 years has not been assessed by EMA.

Cost-effectiveness

NoMA has assessed the submitted health economic analyses from Vertex. Multiple important limitations and uncertainties in the analyses were identified and remained:

- Patients were only followed for 24 and 8 (+8) weeks in the EVOLVE and EXPAND trials, respectively. Taking into account that the treatment of CF is lifelong, and that EMA (4) recommends a minimum of 12 months study duration for FEV1 endpoint for therapies aiming to slow or stop pulmonary disease progression, NoMA considers the follow-up time in the pivotal trials too short to be able to demonstrate a lasting effect compared to BSC. Additional follow-up data from Study 110 does not provide information about the relative effect since this is a one-armed study. The relative effect after week 24 and 8 is based on external data and assumptions.
- The UK CF registry data based on the 1985–2008 birth CF cohorts (not genotype-specific) were used for a reference survival curve in both models (F/F and F/RF genotypes). The survival curve is not fully representative of the Norwegian population; the distribution of genotypes varies between the countries and the curves likely underestimate the survival as early diagnosis, BSC and prognosis have improved in recent years. The pooled CF survival curve may not be plausible as the literature suggests that CFTR mutations are independent predictors of survival on a group level. NoMA would have preferred genotype-specific reference curves but has still accepted UK CF cohorts data as the reference curve does not seem to affect the results to a large extent.
- The input values for the model are often based on highly uncertain estimates (broad confidence intervals due to low event numbers) sourced from external trials.
- ppFEV1 is the key parameter in the model as it affects survival, the pulmonary exacerbation (PEx) equation, as well as the utility equation. Nevertheless, the model outputs in terms of ppFEV1 (and subsequently PEx) are very difficult to validate against available CF registries. Furthermore it is not possible to validate modelled ppFEV1 and PEx results for TEZ/IVA against 96 week follow-up data from Study 110.
- Relative effect size is based on a 100% compliance rate for TEZ/IVA. However, costs in the model correspond to an 80% compliance rate.
- In the models, 14.3% and 8.1% of the patients discontinue treatment after 24 and 8 weeks (i.e. duration of the EVOLVE and EXPAND studies). Thereafter it is assumed in both models that all patients will continue treatment with TEZ/IVA for as long as they live. Follow-up data form Study 110 show that 13.5% of included F/F and F/RF patients had discontinued TEZ/IVA after 96 additional weeks of therapy, and this is not accounted for in Vertex's base-case from 22nd of Ocotber 2019.
- The choice of the health-related quality of life instrument was not sufficiently justified, nor was the utility estimation approach.

Utility weights used in the model for CF patients are high, and somewhat higher than what would be expected for a severe disease like CF. The main driver of the utility gain is life years gained with TEZ/IVA treatment, rather than improved health-related quality of life. A scenario analysis using lower utility weights for more severe FEV1 health states increased the ICER.

In summary, the TEZ/IVA trials primarily inform the model on baseline characteristics (phenotype) and relative effect for a limited period (8 and 24 weeks). Effect parameters for later time points are derived from external sources and assumptions. This makes it very difficult to validate the model results.

NoMA has chosen to make only a few changes to the model, this is in part due to the lack of better estimates, and in part because the model is not sensitive to many of the wanted changes, a consequence of the high drug costs which are the major driving factor for the results. The monthly costs of TEZ/IVA is about 130 000 NOK.

Four parameters have been changed in NoMA's own analyses based on the Vertex's model submitted on the 22nd of October 2019:

- F/F patient population from the TEZ/IVA EVOLVE study, rather than both the EVOLVE study and the LUM/IVA studies TRAFFIC and TRANSPORT.
- TEZ/IVA and IVA drug prices kept unchanged throughout the analysis period, and not reduced due to the introduction of generic pharmaceuticals.
- Health related quality of life increment for patients in the TEZ/IVA arm compared to patients in the BSC arm not included.
- TEZ/IVA discontinuation rate of 13.5% based on 96 week follow-up data from Study 110 included.

NoMA's base-case for the F/F population results in the following:

	TEZ/IVA	BSC	Difference
Total costs	NOK 17 088 785	NOK 3 332 132	NOK 13 756 653
Total QALYs	9.40	7.76	1.63
Total life years	12.64	10.68	1.96
Incremental cost per QALY gained			**NOK 8 416 427**
Incremental cost per life year gained			NOK 7 008 588

Vertex's base-case for the F/F population results in the following:

- Incremental cost per QALY gained: NOK 4 304 115
- Incremental cost per life year gained: NOK 4 304 971

NoMA's base-case for the F/RF population results in the following:

	TEZ/IVA	BSC	Difference
Total costs	NOK 16 054 145	NOK 2 760 232	NOK 13 293 912

Total QALYs Total life years	8.43 11.07	6.44 8.85	1.98 2.23
Incremental cost per QALY gained Incremental cost per life year gained			**NOK 6 699 338** NOK 5 973 491

Vertex's base-case for the F/RF population results in the following:

- Incremental cost per QALY gained: NOK 3 864 038
- Incremental cost per life year gained: NOK 4 134 676

Budget impact
NoMA estimated the budget impact for the specialist health services to be around 140 million NOK including VAT in the fifth year after introduction if all eligible adult patients with CF and F/F or F/RF genotype are treated with TEZ/IVA.

NoMA´s overall assessment
NoMA has identified multiple important limitations and uncertainties in the analysis that remained. The studies were considered too short to be able to justify a lasting treatment effect over the time horizon, the input parameters were uncertain and often sourced from external trials, external validation of model outputs could not be conducted, the choice of the health-related quality of life instrument was not sufficiently justified, nor was the utility estimation approach. NoMA considers the estimated gain in overall and quality-adjusted survival for TEZ/IVA compared to BSC to be highly uncertain. Even after additional follow-up data was submitted it is difficult to evaluate the long-term outcomes of TEZ/IVA.

SAMMENDRAG

Metode
Hurtig metodevurdering av legemiddelet tezakaftor/ivakaftor (TEZ/IVA, Symkevi) i kombinasjon med ivakaftor (IVA, Kalydeco) til behandling av pasienter ≥12 år med cystisk fibrose (CF). Legemiddelverket har vurdert prioriteringskriteriene knyttet til nytte, ressursbruk og alvorlighet ved bruk av TEZ/IVA i henhold til godkjent preparatomtale, og bestilling ID2018_112: Kombinasjonsbehandling tezakaftor/ivakaftor morgen og ivakaftor (Kalydeco) kveld hos pasienter med cystisk fibrose.

Vurderingen tar hovedsakelig utgangspunkt i dokumentasjon innsendt av Vertex.

Bakgrunn
CF er en autosomal, ressesiv, arvelige sykdom, med kroniske forverrelser av kliniske sykdomstegn og kortere levetid sammenlignet med den friske befolkningen. Det finnes ingen kur for CF. CF forårsakes av mutasjoner i CFTR genet, dette resulterer i manglende eller svekket funksjon av CFTR (Cystic Fibrosis Transmembrane conductance Regulator) proteiner på celleoverflaten. CFTR proteiner er epitale kloridkanaler involvert i reguleringen av salt og vann. CF er assosiert med multiorgansvikt grunnet sviktende kloridtransport i organene. Det er påvist svært mange mutasjoner som kan gi CF. Noen regnes for å være milde, mens andre gir alvorlig sykdom. Av de europeiske pasientene, har ca. 40 % en dobbel kopi av F508del (dvs homozygot, F/F). På gruppenivå har pasienter med F/F-mutasjon svært dårlig eller manglende CFTR funksjon. Pasienter er heterozygote for F508del mutasjonen dersom de har en kopi av F508del og i tillegg en annen mutasjon som koder for restfunksjon (dvs F/RF). Disse pasientene har en noe bedre CFTR funksjon enn F/F-pasientene. TEZ/IVA er CFTR-modulatorer til behandling av den kausale årsaken til CF hos pasienter med F/F-mutasjon, samt 14 spesifiserte F/RF-mutasjoner.

Pasientgrunnlag i Norge
Årlig antas det å være omtrent 110 pasienter med F/F-mutasjon, og 30 pasienter med en F/RF-mutasjon som er aktuelle for behandling med TEZ/IVA i Norge. Pasientantallet forventes å være stabilt de kommende årene.

Alvorlighet og prognosetap
Alvorlighetsgraden kan påvirke om kostnadene vurderes å stå i rimelig forhold til nytten av behandlingen. Legemiddelverket har beregnet at CF for denne populasjonen behandlet med standard støttebehandling har et absolutt prognosetap (APT) på ca. 30 og 28 QALY for hhv F/F og F/RF gruppene.

Behandling i norsk klinisk praksis
Standard støttebehandling (BSC) er grunnlaget for CF-behandling. Norge følger europeiske behandlingsretningslinjer og har også utviklet egne nasjonale retningslinjer (1-3). Det primære målet med BSC er å bremse tap av lungefunksjon, opprettholde god ernæringsstatus og behandle komorbiditeter.

CFTR-modulatorene IVA monoterapi og lumakaftor/ivakaftor (LUM/IVA, Orkambi) er i bruk hos norske pasienter med visse genotyper av CF. Per i dag er det imidlertid ingen CFTR-modulator tilgjengelig for behandling av F/RF-genotype, og disse pasientene behandles med BSC alene. LUM/IVA har godkjent indikasjon til behandling av pasienter med F/F-genotype, og 30 norske pasienter behandles med LUM/IVA

i dag. LUM/IVA er imidlertid ikke metodevurdert i Norge, og det er ikke avklart om LUM/IVA er kostnadseffektiv. Legemiddelverket vurderer at BSC er relevant komparator i begge pasientgruppene; både F/F- og F/RF genotype. I tillegg har Legemiddelverket vurdert relativ effekt mellom TEZ/IVA og LUM/IVA for F/F- populasjonen.

Effektdokumentasjon i henhold til norsk klinisk praksis

Klinisk effekt og sikkerhet av TEZ/IVA er undersøkt i to randomiserte kontrollerte fase III -studier:

- F/F-populasjon: den 24 uker lange EVOLVE studien (N = 510)
- F/RF-populasjon: den 8 (+8) uker lange cross-over studien EXPAND (N = 248)

Studiene undersøkte relativ effekt av TEZ/IVA + BSC sammenlignet med BSC alene. Pasientene fra EVOLVE og EXPAND kunne fortsette i den enarmede oppfølgingsstudien, studie 110, hvor samtlige pasienter fikk TEZ/IVA i 96 uker. Disse studiene er nå avsluttet. Endelige oppfølgingsdata fra studie 110 ble gjort tilgjengelige for Legemiddelverket 22. oktober 2019.

EVOLVE og EXPAND studiene viste statistisk signifikante forbedringer i lungefunksjon (dvs for det primære endepunktet ppFEV1) i favør av behandling med TEZ/IVA sammenlignet med BSC alene. Oppfølgingsdata fra studie 110 viser at bedringen av lungefunksjon ble opprettholdt i 96 ekstra uker for pasienter med F/RF mutasjon, og for pasienter med F/F mutasjon var lungefunksjonen forbedret sammenlignet med baseline. Studie 110 kan ikke informere om relativ effekt ettersom den mangler en komparator-arm (BSC).

Det ble vist en statistisk signifikant forbedret rate for pulmonære eksaserbasjoner (PEx) i favør av TEZ/IVA i EVOLVE studien (F/F-populasjon). PEx var et eksplorativt endepunkt i EXPAND studien (F/RF-populasjon), og resultatene fra denne studien er derfor kun deskriptive. Det ble vist en positiv trend i retning forbedret PEx rate i favør av TEZ/IVA. Etter ytterligere 96 uker med TEZ/IVA behandling i Studie 110 var trenden for PEx rate positiv for både F/F og F/RF populasjonene.

TEZ/IVA studiene vurderes som relevante for norsk klinisk praksis.

Effekt hos barn under 12 år er ikke vurdert av EMA.

Sikkerhet
De vanligste bivirkningene hos pasienter behandlet med TEZ/IVA i sammenslåtte data fra fase III studiene var hodepine (14% versus 12% for placebo) og nasofaryngitt (12% versus 10% for placebo).

Sikkerhet hos barn under 12 år er ikke vurdert av EMA.

Kostnadseffektivitet
Legemiddelverket har vurdert den innsendte helseøkonomiske analysen fra Vertex. Det er identifisert flere viktige begrensninger og usikkerheter ved analysen:

- Pasientene ble kun fulgt i 24 og 8 (+8) uker i EVOLVE og EXPAND studiene. Behandling av CF er livslang, og EMA (4) anbefaler minimum 12 måneders oppfølgingstid for utfallsmålet FEV1 i studier av behandlinger som har som mål å bremse sykdomsprogresjon i lungene.

Legemiddelverket vurderer derfor at oppfølgingstiden i de pivotale studiene er for kort til å anta en varig mereffekt av TEZ/IVA sammelignet med BSC. Ytterligere oppfølgingsdata fra studie 110 gir ikke tilstrekkelig informasjon om relative effekt ettersom dette er en enarmet studie. I modellen er relativ effekt etter uke 24 og 8 basert på eksterne data og antagelser.

- Registerdata fra UK basert på fødselskohortene 1985-2008 er brukt som referansekurve for overlevelse i begge modellene (F/F- og F/RF-genotyper). Overlevelseskurven er ikke fullt ut representativ for norske forhold; distribusjonen av genotyper varierer mellom landene og kurven underestimerer sannsynligvis overlevelse ettersom tidlig diagnostikk, BSC og prognoser har bedret seg de senere år. En sammenslått overlevelseskurve for alle genotyper er trolig ikke plausibel som proxy for spesifikke genotyper, ettersom litteraturen peker på at ulike CFTR mutasjoner er uavhengige prediktorer for overlevelse på gruppenivå. Legemiddelverket hadde foretrukket å benytte genotype-spesifikke overlevelseskurver i modellen, men har likevel akseptert bruken av registerkurven ettersom denne fungerer som en referansekurve som tilsynelatende ikke påvirker resultatene i betydelig grad.
- Input-data for effekt i modellen er i stor grad basert på svært usikre estimater hentet fra eksterne studier.
- Lungefunksjon (ppFEV1) er en nøkkelparameter i modellen ettersom den påvirker overlevelse, pulmonære eksaserbasjoner (PEx) og helserelatert livskvalitet. Det er imidlertid ikke mulig å validere modellens resultater for ppFEV1 og PEx mot tilgjengelige CF registre og mot 96 ukers oppfølgingsdata fra Studie 110.
- For TEZ/IVA er relativ effekt i modellene basert på en antagelse om 100 % compliance, mens kostnader er beregnet basert på en compliance rate på 80 %.
- I modellene avslutter 14,3% og 8,1% av pasientene behandling med TEZ/IVA etter 24 og 8 uker (som observert i EVOLVE og EXPAND studiene). Etter dette antas det at samtlige pasienter behandles med TEZ/IVA så lenge de lever. Oppfølgingsdata fra Studie 110 viser imidlertid at ytterligere 13,5% av de inkluderte F/F- og F/RF-pasientene hadde avsluttet TEZ/IVA behandlingen ved 96 uker, og dette tas det ikke høyde for i Vertex' basecase av 22. oktober 2019.
- Valg av instrument for måling helserelatert livskvalitet og metoden for å estimere helsenytte er ikke tilstrekkelig begrunnet.

Nyttevektene for CF pasienter som benyttes i modellen er høye, og også høyere enn hva man kanskje kan forvente ved en alvorlig sykdom som CF. Hoveddriveren for nyttegevinst er modellens resultat for vunnede leveår ved TEZ/IVA-behandling, heller enn forbedret helserelatert livskvalitet. Dette vises i scenarioanalyser. Ved å benytte lavere nyttevekter for mer alvorlige FEV1 helsetilstander øker IKER.

Oppsummert benyttes TEZ/IVA studiene i modellene primært til å informere om pasientenes baseline karakteristika (fenotype) og relativ effekt for en begrenset periode på 8 og 24 uker. Estimater for effekt ved senere tidspunkter er hentet fra eksterne kilder eller baserer seg på antagelser. Dette gjør det vanskelig å validere modellenes resultater.

Legemiddelverket har valgt å gjøre få endringer i modellen. Dette skyldes dels at vi mangler andre, bedre dokumenterte estimater, og dels at legemiddelkostnaden for TEZ/IVA er så høy at den i seg selv er en sterkt drivende faktor av IKER. Den månedlige legemiddelkostnaden for TEZ/IVA er rundt 130 000 NOK.

Modellresultatene som vises under tar utgangspunkt i Vertex' sitt basecase fra 22. oktober 2019.

Fire parametre har blitt endret i Legemiddelverkets analyse:

- F/F pasientpopulasjon fra TEZ/IVA-studien EVOLVE alene, heller enn fra både EVOLVE og LUM/IVA-studiene TRAFFIC og TRANSPORT.
- Legemiddelkostnadene for TEZ/IVA og IVA holdes uendret gjennom analyseperioden, og reduserers ikke ved introduksjon av generiske konkuranse.
- Det appliseres ikke nyttepåslag på 0,043 for pasienter i TEZ/IVA armen sammenlignet med pasienter i BSC armen.
- En seponeringsrate for TEZ/IVA tilsvarende 13,5% i løpet av 96 uker er lagt til, basert på oppfølgingsdata fra Studie 110.

Legemiddelverkets basecase med resultater for F/F populasjon:

	TEZ/IVA	BSC	Differanse
Totale kostnader (NOK)	NOK 17 088 785	NOK 3 332 132	NOK 13 756 653
Totale QALYs	9.40	7.76	1.63
Totale leveår	12.64	10.68	1.96
Merkostnad (NOK) per vunnet QALY			**NOK 8 416 427**
Merkostnad (NOK) per vunnet leveår			NOK 7 008 588

Vertex scenario uten Legemiddelverkets endringer, resultater for F/F populasjon:

- Merkostnad (NOK) per vunnet QALY: NOK 4 304 115
- Merkostnad (NOK) per vunnet leveår: NOK 4 304 971

Legemiddelverkets basecase med resultater for F/RF populasjon:

	TEZ/IVA	BSC	Differanse
Totale kostnader (NOK)	NOK 16 054 145	NOK 2 760 232	NOK 13 293 912

Totale QALYs Totale leveår	8.43 11.07	6.44 8.85	1.98 2.23
Merkostnad (NOK) per vunnet QALY Merkostnad (NOK) per vunnet leveår			**NOK 6 699 338** NOK 5 973 491

Vertex scenario uten Legemiddelverkets endringer, resultater for F/RF populasjon:

- Merkostnad (NOK) per vunnet QALY: NOK 3 864 038
- Merkostnad (NOK) per vunnet leveår: NOK 4 134 676

Budsjettkonsekvenser

Basert på data og antagelser over har det blitt estimert at å behandle aktuelle pasienter med CF og F/F eller F/RF med TEZ/IVA vil ha en total årlig budsjettkonsekvens på 140 millioner NOK inkl mva i det femte budsjettåret. Budsjettberegningene er usikre og forenklede.

Legemiddelverkets vurdering

Legemiddelverket har identifisert flere viktige begrensninger og usikkerheter i den helseøkonomiske analysen. TEZ/IVA studiene vurderes å ha for kort varighet til å kunne anta den langtidseffekten som modellen estimerer, input-data for effekt er usikre og ofte basert på andre kilder enn TEZ/IVA-studiene, det er ikke mulig å validere modellens resultater mot eksterne kilder, valg av instrument for måling helserelatert livskvalitet og metoden for å estimere helsenytte er ikke tilstrekkelig begrunnet. Legemiddelverket vurderer at den estimerte gevinsten i totaloverlevelse og kvalitetsjusterte leveår for TEZ/IVA er høyst usikker. Selv etter at Vertex har leverte nye oppfølgingsdata er det vanskelig å evaluere langtidseffekt av TEZ/IVA i modellen.

FOLKELIG SAMMENDRAG

VURDERING AV SYMKEVI

Hva er en metodevurdering? Du kan lese om Legemiddelverkets arbeid med metodevurderinger *her*

Hva menes med et *godt leveår*? Du kan lese mer om hva som menes med et godt leveår *her*

Hva er Cystisk Fibrose? Du kan lese om Cystisk fibrose på *helsenorge.no*

https://helsenorge.no/sykdom/sjeldne-diagnoser/cystisk-fibrose

Hva er Symkevi?
Symkevi er et legemiddel som kan bremse tap av lungefunksjon hos pasienter som har sykdommen Cystisk Fibrose (CF) med noen spesielle genetiske mutasjoner. Symkevi øker mengden og effektiviteten av et protein kalt CFTR (*cystisk fibrose transmembran konduktansregulator*) på celleoverflaten. Dette proteinet er skadet hos noen personer med CF som har en mutasjon i *CFTR*-genet. Symkevi brukes i kombinasjon med et annet legemiddel mot CF som heter Kalydeco.

Hvor alvorlig er sykdommen?
CF er en sykdom som rammer veldig ulikt. CF med de spesielle genetiske mutasjonene er en mer alvorlig tilstand. Personer med denne formen for CF lever ofte kortere og har oftere dårligere livskvalitet enn personer med andre former for CF.

Hvor mange pasienter finnes det i Norge som kan få behandling med Symkevi?
Omtrent 140 personer i Norge har CF med de spesielle genetiske mutasjonene. Bare disse pasientene er aktuelle for behandling med Symkevi og Kalydeco i kombinasjon.

Hvilken nytte har Symkevi?
Symkevi gjør at lungecellene fungerer bedre hos noen personer med CF. Dette bremser tap av lungefunksjon og gir bedre livskvalitet hos noen. Symkevi kan utsette sykdomsforverring, og Legemiddelverket har beregnet at Symkevi kan øke gjennomsnittlig levetid med om lag 2 år. Enkeltpersoner vil ha mindre eller større nytte av behandlingen enn gjennomsnittet. For de fleste av disse pasientene finnes det ingen andre legemidler mot denne sykdommen i dag, og det er sammenlikningsgrunnlaget når vi vurderer nytten av Symkevi.

Hvordan er nytten av behandlingen undersøkt?
Nytten av og risikoen ved behandling med både Symkevi og Kalydeco er undersøkt i to kliniske studier. I disse studiene ble pasientene trukket ut til å få behandling enten med Symkevi og Kalydeco eller med placebo (juksemedisin). Etter 8 uker i en studie og 24 uker i en annen studie, var lungefunksjon bedre hos pasientene som hadde fått behandling med Symkevi og Kalydeco enn hos pasientene som hadde fått placebo. Pasientene ble behandlet og fulgt opp i til sammen 2 år, og lungefunksjonen var stabil gjennom denne oppfølgingsperioden.

Legemiddelfirmaet Vertex har laget en modell for å beregne hvordan behandling med Symkevi og Kalydeco påvirker pasientenes lungefunksjon, levetid og livskvalitet. Modellen prøver å forutsi hvilken effekt behandlingen har så lenge pasientene lever. Modellen beregner levetid og sykdomsforløp for personer med CF basert på en studie av en gruppe engelske pasienter med CF.

Legemiddelverkets vurdering av dokumentasjonen
Legemiddelverket har vurdert studiene og beregningsmodellen som legemiddelfirmaet Vertex har laget.

Forbedret og stabil lungefunksjon er viktig for å bremse sykdomsforverring. Studiene viser forbedret lungefunksjon i inntil 2 år, altså det tidsrommet som er studert. Samtidig er CF en sammensatt sykdom, og flere faktorer påvirker sykdommen og hvor god helse pasienten har. Det er mye vi ikke vet om CF. Vi har vurdert en rekke antakelser som legemiddelfirmaet har gjort for å forutsi i hvor stor grad personer med CF vil ha nytte av behandlingen om for eksempel 10, 20 eller 30 år.

Legemiddelverket mener det er vanskelig å vurdere hvilken nytte behandlingen med Symkevi og Kalydeco vil ha for norske pasienter over tid. Det er fordi dokumentasjonen har noen svakheter:

- Kort oppfølgingstid i studiene – vi vet for lite om effekten av legemidlet utover de to årene studiene varte.
- Bruk av registerdata fra Storbritannia, der andre genetiske forhold i befolkningen kan påvirke hvor lenge pasienter lever med sykdommen.
- Bruk av registerdata fra en eldre aldersgruppe som har hatt tilgang til forsinket/dårligere diagnostikk og behandling enn yngre pasientgrupper.
- I oppfølgingsperioden fikk alle pasientene i studiene Symkevi og Kalydeco. Vi kan ikke vurdere hvilken effekt Symkevi faktisk har på pasientene i denne perioden uten å sammenlikne med sykdomsutviklingen hos pasienter som fikk placebo (juksemedisin).

Legemiddelverket mener dessuten at legemiddelfirmaet har gjort en rekke antakelser om fremtidige kostnader og nytte som vi ikke kan godta:

1) Legemiddelfirmaet antar at prisen på Symkevi og Kalydeco vil falle om 11 år på grunn av mulig konkurranse av kopipreparater når patentet utløper. Det er vanskelig å forutsi når og om det kommer et kopipreparat og hva dette vil koste. Vår kostnadsvurdering baserer seg på at Symkevi og Kalydeco vil ha samme pris gjennom hele livsløpet.
2) Legemiddelfirmaet antar at behandlingen i seg selv gir en bedre livskvalitet uavhengig av om sykdommen bremses. Vi mener dette ikke er dokumentert, og antar at effekten hovedsakelig skyldes at behandlingen bremser sykdomsutviklingen.

Hvor mye koster Symkevi?
En måneds legemiddelbehandling med Symkevi og Kalydeco koster i dag 130 000 kroner. Dette kommer i tillegg til kostnader til annen behandling og oppfølging i helsetjenesten, slik som fysioterapi. Disse kostnadene vil påløpe uavhengig om pasientene får behandling med Symkevi og Kalydeco eller ikke.

Hva er forholdet mellom nytte og kostnad?
Dokumentasjonen tyder på at pasienter som behandles med Symkevi kan få noe lengre levetid og noe bedre livskvalitet. Likevel er effekten sannsynligvis begrenset, og det må vi ta hensyn til når vi vurderer forholdet mellom nytte og kostnad.

Legemiddelprisen per pasient er om lag 130 000 kroner per måned. Det tilsvarer 13,5 millioner kroner dersom pasienten behandles i 13 år.

For å vurdere nytte og kostnad ved bruk av Symkevi må vi regne om prisen til det vi kaller kostnaden for et «godt leveår» (på fagspråket kalt «kvalitetsjustert leveår»). Med et godt leveår mener vi ett år helt uten sykdom. Dette er en standardisert måte å regne på som gjør det mulig å sammenlikne nytten av ulike behandlinger som brukes mot ulike sykdommer.

Selv med god behandling vil ikke sykdommen kureres. En person med CF vil derfor kunne oppleve lavere livskvalitet enn en person helt uten sykdom, og vil dermed få færre «gode leveår» sammenliknet med antall år hun/han faktisk lever. En pasient som behandles med Symkevi kan i regne med å forlenge livet med igjennomsnitt to «gode leveår». Vi antar at kostnaden for et «godt leveår» ved behandling med legemidlet vil være rundt 7 millioner kroner, eller cirka 13,5 millioner for to «gode leveår».

Hvem bestemmer om Symkevi skal tas i bruk?
Legemiddelverkets rolle i evalueringen av sykehusmedisiner er å gi et estimat av forholdet mellom nytte og kostnad, altså kostnaden for et «godt leveår». Hvor mye det norske samfunnet er villig til å betale for et «godt leveår» er avhengig av hvor alvorlig sykdommen er. Beslutningsforum, bestående av direktørene for helseforetakene, fatter en endelig beslutning om innføring av nye behandlinger i norske sykehus.

TABLE OF CONTENTS

LOGG

Bestilling:	ID2018_112: Kombinasjonsbehandling tezakaftor/ivakaftor morgen og ivakaftor (Kalydeco) kveld hos pasienter med cystisk fibrose
Forslagstiller:	Statens legemiddelverk
Legemiddelfirma:	Vertex Pharmaceuticals AB
Preparat:	Symkevi i kombinasjon med Kalydeco
Virkestoff:	Tezakaftor/ivakaftor i kombinasjon med ivakaftor
Indikasjon:	Behandling av pasienter med cystisk fibrose (CF) som er 12 år eller eldre og homozygot for F508del mutasjon eller som er heterozygot for F508del mutasjon og har en av følgende mutasjoner i cystic fibrosis transmembrane conductance regulator (CFTR) genet: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.
ATC-nr:	R07AX31

Prosess

Dokumentasjon bestilt av Legemiddelverket	14-12-2017
Fullstendig dokumentasjon mottatt hos Legemiddelverket	21-12-2018
Klinikere kontaktet for første gang	29-03-2019
LIS kontaktet for første gang av Legemiddelverket	12-02-2019
Legemiddelverket bedt om ytterligere dokumentasjon	07-05-2019
Ytterligere dokumentasjon mottatt av Legemiddelverket	07-06-2019
Oppfølgingsdata mottatt av Legemiddelverket	22-10-2019
Rapport ferdigstilt:	07-02-2020
Saksbehandlingstid:	464 dager hvorav 123 dager i påvente av ytterligere opplysninger fra legemiddelfirma. Dette innebærer en reel saksbehandlingstid hos legemiddelverket på 290 dager.
Saksutredere:	Einar Andreassen Reidun Os Husteli Yvonne Anne Michel Ania Urbaniak
Kliniske eksperter:	Olav T. Storrøsten Diane M. Snowdon Atle R. Riise Pål L. Finstad

Kliniske eksperter har bidratt med avklaringer av sentrale forutsetninger i analysen (bl.a. sammenlignende behandling, pasientgrunnlag og overførbarhet av studiedata til norsk klinisk praksis). I arbeidet med rapporten har klinikere deltatt på møte med Legemiddelverket og hatt muntlig og skriftlig kommunikasjon med saksbehandlere. Ved ferdigstillelse av rapporten har klinikere bekreftet sine utsagn som er brukt i rapporten. Legemiddelverket er ansvarlig for rapportens innhold. Kliniske eksperter har ikke hatt noen formell «peer-review» funksjon ved utarbeidelse av rapporten.

GLOSSARY

AE	Adverse Event
AUP	Apotekenes Utsalgspris, Pharmacy Retail Price
BSC	Best Supportive Care
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane conductance Regulator
CI	Confidence Interval
CUA	Cost-Utility Analyses
DCO	Data Cut-Off
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
FEV_1	Forced Expiratory Volume per second
F/F	Homozygous F508del mutation
F/RF	Heterozygous F508del mutation with a Residual Function mutation in the other allele
FVC	Forced Vital Capacity
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
GI	Gastrointestinal
ICU	Intensive Care Unit
IRC	Independent Review Committee
ITC	Indirect Treatment Comparison
IV	Intravenous
Iva	Ivacaftor
KM	Kaplan-Meier
LUM	Lumacaftor
MEM	Mixed-Effects Model
MMRM	Mixed-Effects Model for Repeated Measures
MPR	Medication Possession Ratio
NoMA	Norwegian Medicines Agency
OLE	Open Label Extension
OS	Overall Survival

PA	Pseudomonas Aeruginosa
PRP	Pharmacy Retail Price
ppFEV$_1$	percent predicted FEV$_1$
QALY	Quality Adjusted Life Year
RF	Residual Function
SmPC	Summary of Product Characteristics
STA	Single Technology Assessment
TEZ	Tezacaftor

1 BACKGROUND

1.1 SCOPE

This single technology assessment (STA) assesses the treatment with tezacaftor/ivacaftor (TEZ/IVA, trade name Symkevi) in combination with ivacaftor (IVA, Kalydeco) for patients ≥12 years with Cystic Fibrosis (CF) in Norway.

Health service interventions are evaluated against the three prioritisation criteria in Norway; the benefit criterion, the resource criterion, and the severity criterion. Effect and safety of TEZ/IVA[1] in the treatment of CF have been examined in the randomised, controlled, phase 3 trials EVOLVE and EXPAND, and the open, uncontrolled follow-up Study 110. TEZ/IVA combined with best supportive care (BSC) is compared to BSC alone in a cost-utility analysis (CUA). A cost-minimisation assessment versus lumacaftor/ivacaftor (LUM/IVA, Orkambi) has also been undertaken. NoMA´s assessment is primarily, but not exclusively, based on the documentation presented by Vertex.

NoMA received documentation for the STA from Vertex 21-Dec-2018. NoMA received updated follow-up data from Study 110 on 22-Oct-2019.

TEZ/IVA is a CFTR (Cystic Fibrosis Transmembrane conductance Regulator) modulator treatment for CF. Up to this point, two other CFTR modulators with Marketing Authorisation (MA) have been used in Norway, Kalydeco and Orkambi. Both Kalydeco and Orkambi have been used based on individual reimbursement paid by The Norwegian Health Economics Administration (HELFO) after application. According to HELFO, 15 and 30 patients respectively used Kalydeco and Orkambi in 2018. The treatment with Kalydeco and Orkambi has not been previously assessed against the prioritisation criteria, and it has not been established whether these treatments are cost effective. From the 1st of February 2019 the regional hospital enterprises are responsible for the funding of these drugs. STAs for Symkevi (ID2018_112), Kalydeco monotherapy (ID2018_110) and Orkambi (ID2018_111) have been ordered. To date, NoMA has only received documentation to conduct an assessment of Symkevi.

1.2 CYSTIC FIBROSIS

Cystic Fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality, and at present, there is no cure. In total approximately 350-375 patients live with CF in Norway today, where the majority of patients over the age of 18 years (1, 5, 6). The median life expectancy for patients born in 2010 is expected to be about 40 years. Life expectancy has increased over the latest decades, and an increase is predicted to continue (7).

[1] The abbrevation TEZ/IVA in this context applies to the marketed regime tezacaftor/ivacaftor (morning) in combination with ivacaftor (evening), i.e. Symkevi (morning) in combination with Kalydeco (evening).

CF is caused by mutations in the CFTR gene that result in the absence or deficient function of the CFTR (Cystic Fibrosis Transmembrane conductance Regulator) protein at the cell surface. Two mutations (in two alleles, from two carriers) is needed for CFTR deficiency, and the severity of CF is, among several things, dependent on the specific mutations present. The CFTR protein is an epithelial chloride channel responsible for regulating salt and water absorption and secretion. The failure to regulate chloride transport in organs results in the multisystem pathology associated with CF: an accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration. Lung disease is the primary cause of morbidity and mortality in patients with CF (8). The mucus can be difficult to remove, which may lead to chronic respiratory disease and/or insufficient pancreatic effects associated with malnutrition, and etc (4, 8).

Mucus leads to congestion of particles and bacteria in the upper and lower respiratory tract, such as chronic colonisation of pathogenic strains of *Staphylococcus aureus* (SA) and/or *Pseudomonas aeruginosa* (PA). PA can change character from non-mucoid to mucoid phenotype, and form a biofilm which is resistant to some antibiotics. 6.7% of the Norwegian CF patients have evolved a chronic PA infection before they turn 18 years old (5). PA infections are the direct cause of death for 80% of CF patients. With the gradual progression of CF, $ppFEV_1$ (percent predicted forced expiratory volume, FEV_1) declines over time. In healthy children, FEV_1 would increase with growth, but $ppFEV_1$ would remain more or less constant, at or around 100%. The expected $ppFEV_1$ decline in children with CF would be around 2 %-points per year (4, 8). Progression of CF lung disease is characterised by periods of stability and intermittent episodes of clinical deterioration, termed Pulmonary Exacerbations (PEx). According to "*ECFS best practice guidelines*" there is no agreed definition of PEx (9). Acute exacerbations of the disease may occur at any point in time , but they become more frequent as the disease progresses. Clinical symptoms of exacerbations are fatigue, acute respiratory insufficiency, loss of appetite and weight loss (4, 8).

Many CF patients lose pancreatic function, and this leads to lowered secretion of digestive enzymes, bicarbonate and water, and the following malabsorption of dietary proteins, carbohydrates, and fat. Diabetes mellitus is also associated with the changes in the pancreas (4, 8).
The diagnosis needs to be confirmed by a genetic test and a sweat test (10). For patients born after 2012, CF will be diagnosed if the patient has clinical disease in one or more organs and an elevated level of sweat chloride (≥60 mmol/L). Still, approximately 2% of the patients will have normal levels of sweat chloride despite having met other criteria for CF (8).

Prognosis for individual CF patients varies with the patient's genotype and phenotype. The phenotypical expression (manifestation of CF) in the respiratory system varies, and few (certain) correlations between genotype and pulmonary phenotype are established. There exists a broad spectrum of phenotypes that cannot fully be explained by the relationship to the genotype alone; for instance family members with the same genotype may have different phenotypes. Furthermore, some phenotypical characteristics are linked to each other, for instance, pancreatic insufficiency is strongly correlated with severe lung disease

(11). Even though the relationship between the genotype and phenotypical expression is not fully understood, there is agreement on the underlying cause of CF, namely mutations in the CFTR gene.

Approximately 2000 mutations in the CFTR gene have been identified, but 159 CFTR variants represent 96% of the alleles causing disease (12). There are several systems for classification of CF. For severity based on phenotype, five classes of around 2000 mutations in the CFTR gene have been identified, but 159 CFTR variants represent 96% of the alleles causing disease. (12). The five classes are used to describe which failures the gene mutations cause in the production of the CFTR protein. Overall, CFTR mutation classes I-III are considered to cause more severe illness and insufficient pancreatic function than classes IV and V (12). The accuracy of using CFTR genotype as a predictor of morbidity and mortality is still debatable.

The most prevalent mutation is an in-frame deletion in the CFTR gene resulting in a loss of phenylalanine at position 508 in the CFTR protein (F508del-CFTR). This is a class II mutation. In people with this mutation, a full length of protein is transcribed, but recognised as misfolded by the cell and degraded before reaching the cell membrane, where it needs to be positioned to effect transepithelial salt transport. This severe mutation is associated with no meaningful CFTR function (13). Patients with a double copy of F508del are homozygotes (F/F) and consitute approximately 40% of European CF patients. Patients who have an F/F mutation are considered to suffer from a severe form of CF disease.

Patients with one copy of F508del are heterozygotes, and if they have another mutation coding for CFTR-defect they may be diagnosed with compound heterozygous CF. The presence of an allele coding for residual function (RF) is associated with improved nutritional status and pancreatic function compared to patients with F/F mutations, and less severe lung disease (12).

Increasing understanding of how different mutations and combinations of mutations affect the production, structure, and function of CFTR has led to the concept of mutation-specific therapies (13).

The CF population relevant to this STA consists of CF patients ≥12 years with F/F and 14 specific F/RF mutation combinations.

1.3 SEVERITY AND SHORTFALL

The current prognosis for patients with CF is poor.

In Norway, the degree of severity of the condition/disease affects whether the costs are considered reasonable relative to the benefit of the treatment. NoMA has used a quantitative method to calculate the severety of patients with CF. NoMA has estimated that patients ≥12 years with cystic fibrosis have an absolute shortfall of approximately 30 and 28 Quality Adjusted Life Years (QALYs) respectively, for the F/F and F/RF subpopulations.

1.4 TREATMENT OF CYSTIC FIBROSIS

1.4.1 Treatment with tezacaftor/ivacaftor

Therapeutic indication

Tezacaftor 100 mg/ivacaftor 150 mg (Symkevi morning) in combination with ivacaftor 150 mg (Kalydeco evening) is indicated for the treatment of patients with CF aged 12 years and older who are:

- Homozygous for the *F508del* mutation, or
- Heterozygous for the *F508del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.

F/F is used as an abbreviation for patients homozygous for the F508del mutation, and F/RF is used as an abbreviation for heterozygous patients with one F508del allele, and one of the 14 specific RF mutations in the other allele in this STA.

Mechanism of action

CFTR modulators aim to improve the CFTR function, the underlying cause of CF. Tezacaftor is a selective CFTR *corrector* and facilitates the cellular processing and trafficking of normal or multiple mutant forms of CFTR (including F508del-CFTR) to increase the amount of CFTR protein delivered to the cell surface, resulting in increased chloride transport *in vitro*. Ivacaftor is a CFTR *potentiator* that potentiates the channel-open probability (or gating) of CFTR at the cell surface to increase chloride transport.

Posology

The recommended dose for adults and adolescents aged 12 years and older is one tezacaftor 100 mg/ ivacaftor 150 mg tablet taken in the morning and one ivacaftor 150 mg tablet taken in the evening. The dose should be adjusted in certain situations, as described in the Summary of Product Characteristics (SmPC).

Adverse Reactions

The most common Adverse Reactions experienced by patients aged 12 years and older who received tezacaftor in combination with ivacaftor in the pooled, placebo-controlled, phase 3 studies were headache (14% versus 12% on placebo) and nasopharyngitis (12% versus 10% on placebo).

For more information, please refer to the SmPC for Symkevi and Kalydeco (14, 15).

1.4.2 Treatment guidelines

Best Supportive Care (BSC) is the basis of CF-treatment in clinical practice. Norway follows the EU CF-guidelines, and has further developed national recommendations (1-3). The Norwegian Resource Centre for Cystic Fibrosis*, Norsk senter for cystisk fibrose (NSCF)*, provides care and support for patients, their families and other health care service providers. There is general agreement that advice on treatment and management is best provided by a multidisciplinary team at a CF Specialist centre, such as NSCF (2).

There is no available treatment that cures CF today. The primary goal of BSC is to slow down the progression/loss of lung function, maintain nutritional status, and to manage co-complications directly linked to the CFTR dysfunction, such as CF related diabetes mellitus, osteoporosis and renal disease. BSC is symptomatic treatment, but does not have any effect on the CFTR dysfunction itself. Current medical treatment consists of antibiotics, mucoactive drugs, hyperosmotic saline solutions, inhaled bronchodilators and steroids, replacement of pancreatic enzymes (PEP). Physiotherapy, advice on physical activity and daily drainage of lungs are central in treatment (4, 10). As the disease progresses, patients may also be identified as candidates for lung transplantation, and in some cases other organs. CF and treatment of the disease are very complex, and several other treatments may also be considered for an individual patient in addition to, or as a part of, BSC. For the indivicual patient BSC will be changing over time.

CFTR modulators added to BSC have been used in Norwegian clinical practice for patients with certain genotypes. Recently, two CFTR modulators have been licensed in the Norwegian market since 2012. Ivacaftor (Kalydeco) is authorised for the treatment of patients with CF due to gating (class III) mutation in the *CFTR* gene (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R*) and in patients aged 18 years and older who have the *R117H* mutation. The fixed-dose combination of ivacaftor and lumacaftor (Orkambi) is approved for patients homozygous for the F508del mutation, and have been used in Norwegian clinical practice since 2016.

1.4.3 Comparator

BSC is the comparator for Norwegian CF patients heterozygous for F508del with another CFTR mutation with residual function (F/RF). At present no CFTR modulators are available for treating these patients.

Combined treatment with lumacaftor/ivacaftor (Orkambi) has shown clinical effect for the treatment of patients homozygous to F508del mutations (F/F). However, according to clinicians not all patients tolerated this drug due to respiratory events related to lumacaftor. As lumacaftor is a strong inducer of CYP3A (as opposed to ivacaftor and the new CFTR modulator tezacaftor which are substrates of CYP3A), it is not recommended to co-administer certain drugs with lumacaftor (16). In 2018 lumacaftor/ivacaftor was prescribed to 30 Norwegian patients (17). This was financed by individual reimbursement paid by the The Norwegian Health Economics Administration (HELFO) after individual applications. NoMA has never conducted an STA for lumacaftor/ivacaftor. Consequently, cost-effectiveness for this drug has never been established.

In cases where cost-effectiveness for a comparator has not been established, an analysis against such a comparator would usually be insufficent for an STA (18). In such situations, an additional analysis, such as

a comparison against BSC in this STA, needs to be conducted. Therefore, NoMA considers BSC as the key comparator for the F/F population and evaluation of the relative effect vs. LUM/IVA as supplementary to the main analysis.

The main comparator BSC is described in Chapter 1.4.2.

2 RELATIVE EFFECTIVENESS

2.1 OVERVIEW OF RELEVANT CLINICAL STUDIES

2.1.1 Tezacaftor/ivacaftor efficacy studies

Tezacaftor 100 mg/ivacaftor 150 mg (Symkevi, TEZ/IVA[2]) received Norwegian Market Access Authorisation (MAA) on the 31st of October 2018. The main studies that EMA assessed were the following:

- F/F population: the 24-week EVOLVE-trial (also called the 106-trial)
- F/RF population: the 8 + 8-week EXPAND-crossover trial (also called the 108-trial).

EVOLVE and EXPAND are phase 3 randomised controlled trials assessing efficacy and safety of TEZ/IVA plus BSC compared to placebo plus BSC. In addition, Vertex has performed an uncontrolled, open follow-up trial (EXTEND, referred to as Study 110 in this report) which included patients from these trials. Study 110 assessed the long-term safety and tolerability of TEZ/IVA, with efficacy as secondary endpoints.

On the 22nd of October 2019 NoMA received 96 weeks follow up data from Study 110. With the submission of this data Vertex updated their base-case, using Study 110 as input for expected longterm effect of TEZ/IVA on lung function.
The duration of the TEZ/IVA trials were too short to capture long-term effects in general. Although Overall Survival (OS) was not an endpoint in the trials, it was considered to be of importance. Vertex submitted real-world long-term data from UK CF Registry (UKCFR) Annual Data Report 2008 (19) in order to provide further information regarding overall survival, to be used as a reference curve in the model. This data source has previously been used in an HTA of CFTR modulator therapy delivered to NICE (National Institute for Health and Care Excellence) (20).

A Systematic Literature Search (SLR) was undertaken to identify other relevant RCTs reporting effect, safety and PRO/HRQoL (Patient reported outcome/Health related quality of life) for CFTR-modulating therapies in F/F and F/RF populations. For the F/F population the TRAFFIC and TRANSPORT (TT) trials, assessing efficacy and safety for the CFTR modulator combination LUM/IVA were identified. Vertex also submitted an indirect treatment comparison (2.1.3) of TEZ/IVA vs. LUM/IVA, where data from the TT trials and EVOLVE were included.

2.1.2 Ongoing and initiated studies

Table 1 summarizes the trials that were identified as relevant for the STA:

[2] When the abbrevation TEZ/IVA further is used in this STA, the combination regimen where TEZ/IVA morning and iva evening is ment. TEZ/IVA = Symkevi + Kalydeco

Table 1 Overview of relevant ongoing and initiated studies

Trial (acronym, id nr.)	Population	Intervention	Comparator/ control arm	Primary endpoint	Secondary endpoint
NCT02347657 (VX14-661-106, EVOLVE) Blinded phase III trial with parallel groups	Patients ≥12 years with CF, homozygous for F508del-CFTR mutation N=510	Tezacaftor 100mg/ Ivacaftor 150 mg morning and Ivacaftor 150 mg evening for 24 weeks N=251	Placebo morning and evening for 24 weeks N=259	Absolute change in ppFEV1 at week 24	Relative change in ppFEV1, number of PEx, absolute change in BMI and weight, CFQ-R score, safety, absolute change in sweat-chloride. See also comment below table
NCT02392234 (VX14-661-108, EXPAND) Blinded phase III crossover trial	Patients ≥12 years with CF, heterozygous for F508del-CFTR mutation, and another allele with specific CTFR mutations predicted to have residual function (RF) N=248	Tezacaftor 100mg / Ivacaftor 150 mg morning and Ivacaftor 150 mg evening for 8 weeks N=167 *Crossover trial, see* Figure 2	Ivacaftor 150 mg morning and Ivacaftor 150 mg evening for 8 weeks N=164 or Placebo morning and evening for 8 weeks N=165	Absolute change in ppFEV1 at week 4 and week 8	Relative change in ppFEV1, CFQ-R score, safety, absolute change in sweat-chloride. See also comment below table
NCT02565914 (VX14-661-110, EXTEND) Open follow-up trial	Patients from severeal trials, including EVOLVE (N=459) and EXPAND (N=222)	Tezacaftor 100mg/ Ivacaftor 150 mg morning and Ivacaftor 150 mg evening for 96 weeks	None	Safety and tolerance	Absolute change in ppFEV1, number of PEx, absolute change in BMI, absolute change in CFQ-R

No CFTR modulators, including ivacaftor monotherapy, had been approved in subjects with F/RF genotypes before the initiation of the EXPAND study (Figure 2). The ivacaftor control arm in the trial allowed for assessment of the contribution of tezacaftor to ivacaftor. Ivacaftor monotherapy has not been granted MAA for F/RF genotypes based on results from the EXPAND study, and results from this arm will not be presented or evaluated in the STA.

Trial (acronym, id nr.)	Population	Intervention	Comparator/ control arm	Primary endpoint	Secondary endpoint
NCT01807923 (VX12-809-103, TRAFFIC) Blinded phase III trial with parallel groups	Patients ≥12 years with CF, homozygote for F508del-CFTR mutation N=559	Lumacaftor 600mg/ Ivacaftor 250 mg morning and Ivacaftor 250 mg evening for 24 weeks, or Lumacaftor 400mg/ Ivacaftor 250 mg morning and evening for 24 weeks	Placebo morning and evening for 24 weeks	Absolute change in ppFEV1 at week 24	Relative change in ppFEV1, number of PEx, absolute change in BMI and weigth, EQ-5D and CFQ-R score, safety, absolute change in sweat-chloride
NCT01807949 VX12-809-104, TRANSPORT) Blinded phase III trial with parallel groups	Patients ≥12 years with CF, homozygote for F508del-CFTR mutation N=563	Lumacaftor 600mg/ Ivacaftor 250 mg morning and Ivacaftor 250 mg evening for 24 weeks, or Lumacaftor 400mg/ Ivacaftor 250 mg morning and evening for 24 weeks	Placebo morning and evening for 24 weeks	Absolute change in ppFEV1 at week 24	Relative change in ppFEV1, number of PEx, absolute change in BMI and weigth, EQ-5D and CFQ-R score, safety, absolute change in sweat-chloride

CFQ-R= disease specific PRO, Cystic Fibrosis Questionnaire–Revised. Absolute change in ppFEV1 = Absolute percentage change in ppFEV1 from baseline. FEV1 denotes the volume of air that can be exporated per second, measured after full inspiration. RF=Residual function. BMI= Body mass index, kg/m2. EQ-5D = general utility weights

Study VX14-661-106

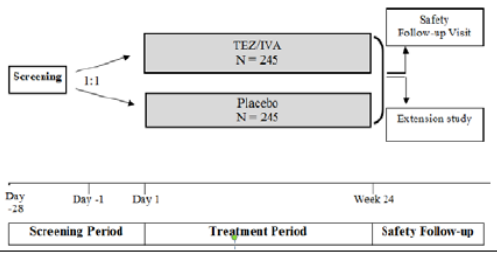
Core efficacy study to support the indication statement

Objectives

- Evaluate the efficacy of TEZ/IVA through Week 24 in F/F subjects
- Evaluate the safety of TEZ/IVA
- Investigate PK of TEZ, M1-TEZ, M2-TEZ, IVA, and M1-IVA

Design

Randomized (1:1), double-blind, placebo-controlled



Population

510 subjects with CF
≥12 years old
Males and females
F/F genotype
ppFEV$_1$ ≥40 to ≤90

Figure 1 Trial design EVOLVE (Study 106) (8)

Study VX14-661-108

Core efficacy study to support the indication statement

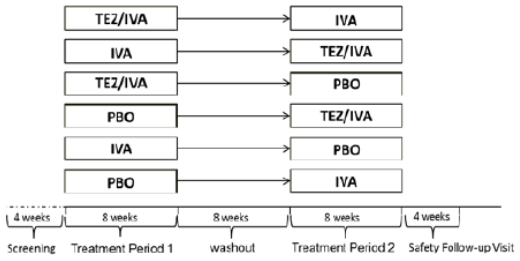
Objectives	Design	Population
• Evaluate the efficacy of TEZ/IVA and IVA monotherapy through 8 weeks of treatment in F/RF subjects • Evaluate safety of TEZ/IVA and IVA monotherapy • Investigate PK of TEZ, M1-TEZ, IVA, and M1-IVA	Randomized (1:1:1:1:1:1), double-blind, placebo-controlled, 2-period, 3-treatment, crossover 	248 subjects with CF ≥12 years old Males and females F/RF genotype ppFEV$_1$ ≥40 to ≤90

Figure 2 Trial design EXPAND (Study 108) (8)

No CFTR modulators, including ivacaftor monotherapy, had been approved in subjects with F/RF genotypes before the initiation of the EXPAND study (Figure 2). The ivacaftor control arm in the trial allowed for assessment of the contribution of tezacaftor to ivacaftor. Ivacaftor monotherapy has not been granted MAA for F/RF genotypes based on results from the EXPAND study, and results from this arm will not be presented or evaluated in this STA.

Table 2 Efficacy endpoints in the EVOLVE (Study 106) and EXPAND (Study 108) trials (8)

Endpoint	Study 106	Study 108
ppFEV$_1$: absolute change	X (primary)	X (primary)
ppFEV1: relative change	X (key secondary)	X (secondary)
PEx: number	X (key secondary)	X (other)
BMI	X (key secondary)	
CFQ-R respiratory domain score	X (key secondary)	X (key secondary)
PEx: time to first	X (secondary)	X (other)
Sweat chloride concentration	X (secondary)	X (secondary)
BMI-z-score	X (secondary)	
Body weight	X (secondary)	
Body weight z-score		
Height z-score		
Rate of change in ppFEV$_1$		
Exocrine pancreatic function		
Serum IRT concentration	X (other)[a]	X (other)
FE-1		X (other)

Sources: Studies 106, 108, 110 CSRs

BMI: body mass index; CRQ-R: Cystic Fibrosis Questionnaire-Revised; FE-1: fecal elastase-1; IRT: immunoreactive trypsinogen; PEx: pulmonary exacerbation; ppFEV1: percent predicted forced expiratory volume in 1 second
Note: Key secondary endpoints are the endpoints that are part of the testing strategy and hence controlled for Type 1 error rate.

From the EVOLVE study a total of 231 (92.0%) subjects in the TEZ/IVA group and 230 (89.1%) study participants in the placebo group rolled over into the treatment cohort of Study 110. From the EXPAND study, 227 (92.3%) study participants enrolled in the treatment cohort of Study 110 (8). Patients from other TEZ/IVA studies were also included in Study 110 (Figure 3). Vertex claims that patients were enrolled directly to Study 110 from parent studies, and patients had no breaks in treatment between studies.

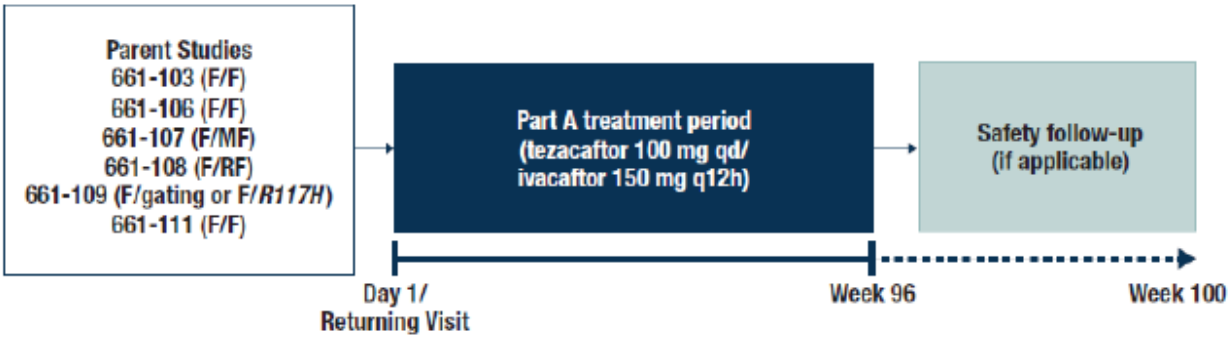


Figure 3 Trial design for the open, uncontrolled follow-up Study 110 (VX14-661-110) (Vertex)

NoMA's assessment of the submitted clinical evidence

The blinding of the studies was considered acceptable by EMA (8).

Patients in both the EVOLVE and EXPAND studies were stratified by age (<18 versus ≥18 years of age), sex and percent predicted FEV1 ($ppFEV_1$) severity determined during the Screening Period (<70 versus ≥70). Patients in the EXPAND study were also stratified according to type of RF mutation for the second CFTR allele (Class V non-canonical splice mutation versus Classes II to IV RF mutation), to ensure enrollment of at least 25% of study participants with Classes II to IV RF mutations. The stratification was considered acceptable by EMA (8).

As the EXPAND study had a 2-period cross-over design, carryover effect and treatment-by-period interaction for the primary analysis were assessed. Carryover effect for the primary analysis was assumed by EMA to be negligible due to the adequately long washout period of 8 weeks (8).

NoMA considers the duration of the EVOLVE and EXPAND studies to be too short to provide sufficient information of the relative effect of TEZ/IVA compared to BSC alone in the health economic analysis where a lifelong perspective is applied. The follow-up single-armed Study 110 can to some degree supplement TEZ/IVA efficacy data for the studied populations. In 2009 EMA (4) recommended a minimum of 12 months study duration for FEV1 endpoint for therapies aiming to slow or stop pulmonary disease progression. In 2016 EMA stated that there is a need for revision of the 2009 guideline on clinical development of medicinal products for the treatment of CF (21). EMA argued that there are elements in the 2009 guideline which are outdated based on the recent advances. However, as the updated guidelines are not yet published, NoMA would refere to the 2009 guideline in its assessment. Hence 96 week follow-

up data from Study 110 is considered long enough to demonstrate effect relative to baseline values for endpoints such as ppFEV1 and PEx. However, this safety study does not provide information about the effect size relative to placebo, and so the total TEZ/IVA study program is not able to inform about relative effect past 24 and 8 weeks (duration of EVOLVE and EXPAND studies, respectively). Taking into account that the treatment of CF is lifelong, 96 + 24/8 weeks (about two years) follow-up data is considered a relatively short time.

2.1.3 Indirect treatment comparison

An Indirect Treatment Comparison (ITC) was conducted using the Bucher's method to compare the efficacy of TEZ/IVA (Symkevi) and LUM/IVA (Orkambi) in the F/F population (Vertex data on file VXMA-HQ-20-00176). In this approach the magnitude of a treatment effect is compared to a common comparator using a 'difference-in-difference' approach; i.e (TEZ/IVA – placebo) – (LUM/IVA – placebo).

The original Marketing Authorization for LUM/IVA in patients aged ≥12 years in the F/F population was granted based on the results from the TRAFFIC and TRANSPORT studies, which both were parallel-group, 24-week placebo-controlled phase 3 studies. The design and conduct of the LUM/IVA trials were almost identical to those for TEZ/IVA in the EVOLVE study, and many of the sites and investigators were the same. Demographic and baseline characteristics were similar across these studies.

The efficacy of TEZ/IVA found in the EVOLVE study was compared to that of the approved dose of LUM/IVA from the pooled analysis of the TRAFFIC and TRANSPORT studies. The indirect comparison was conducted for common endpoints in the TEZ/IVA trials and LUM/IVA trials: absolute change in ppFEV1 at week 24 using Mixed Model Repeated Measurement (MMRM), number of pulmonary exacerbations or change in BMI from baseline. The comparison in terms of absolute change in ppFEV1 through week 24 (the primary endpoint in the EVOLVE study) could not be conducted as such analyses were not performed in the TRAFFIC or TRANSPORT studies.

Both TEZ/IVA and LUM/IVA showed significant and clinically meaningful improvements in ppFEV1 compared to placebo; however, the absolute improvement in ppFEV1 (Least Square, LS, mean treatment difference) [redacted] points greater for TEZ/IVA compared to LUM/IVA. This was statistically significant (p = 0.0079) (Table 3).

Table 3 Indirect comparison of absolute change from baseline in ppFEV1 at week 24, Full Analysis Set.

		TEZ-IVA Study 106		Orkambi TRAFFIC & TRANSPORT	
Analysis	**Statistic**	**TEZ-IVA N = 248**	**Placebo N = 248**	**Orkambi N = 369**	**Placebo N = 371**
	Mean (SD) at Baseline	59.6 (14.7)	60.4 (15.7)	60.5 (14.1)	60.4 (13.8)
	LS Mean (SE)	3.5 (0.5)	-1.3 (0.5)	2.2 (0.4)	-0.4 (0.4)
	P value within Treatment	<0.0001	0.0037	<0.001	0.3494

		TEZ-IVA Study 106		Orkambi TRAFFIC & TRANSPORT	
Absolute change in ppFEV$_1$ from baseline *at* Week 24 MMRM analysis	LS Mean Diff *vs.* Placebo (SE) (95% CI)	4.8 (0.6) (3.6, 6.0)	-	2.6 (0.6) (1.4, 3.7)	-
	P value *vs.* Placebo	<0.0001	-	<0.0001	-
	LS Mean Diff *vs.* Orkambi, 95% CI	[redacted]			
	***P* value *vs.* Orkambi**	[redacted]			

Both TEZ/IVA and LUM/IVA showed significant and clinically meaningful reductions in overall pulmonary exacerbation rates compared to placebo. These rates were comparable for TEZ/IVA (35 % reduction [rate ratio 0.65] and 39 % reduction [rate ratio 0.61] for LUM/IVA) and not statistically different.

There were significant and clinically meaningful reductions in the rate of pulmonary exacerbations requiring i.v. antibiotic and/or hospitalization. Also these rates were not statistically different for TEZ/IVA (47% reduction [rate ratio 0.53] and LUM/IVA with a 56% reduction [rate ratio 0.44] (Table 4 & Table 3).

There was a statistically significant improvement in BMI at 24 weeks for LUM/IVA, but not for TEZ/IVA. The difference between the treatments was however not statistically significant ([redacted]). Absolute change in CFQ-R Respiratory domain scores from baseline at week 24 was significant for TEZ/IVA vs placebo (<0.0001) but not for LUM/IVA vs placebo (p=0.0512). The difference of [redacted] points ([redacted] between TEZ/IVA and LUM/IVA was not significant [redacted].

Table 4 Indirect treatment comparison of secondary (non-lung function) endpoints

		TEZ-IVA Study 106		Orkambi TRAFFIC & TRANSPORT studies	
Analysis	**Statistic**	**TEZ-IVA N = 248**	**Placebo N = 256**	**LUM-IVA N = 369**	**Placebo N = 371**
Number of pulmonary exacerbations through Week 24	Number of Events (Estimated Event Rate per Year)	78 (0.64)	122 (0.99)	152 (0.70)	251 (1.14)
	Rate Ratio vs. Placebo, 95% CI	0.65 (0.48, 0.88)	-	0.61 (0.49, 0.76)	-
	P value vs. Placebo	0.005	-	<0.001	-
	Rate Ratio vs. Orkambi, 95% CI	[redacted]	-	-	-
	P value vs. Orkambi	[redacted]	-	-	-
	Number of Events (Estimated Event Rate per Year)	39 (0.29)	74 (0.54)	65 (0.26)	81 (0.32)
	Rate Ratio vs. Placebo, 95% CI	0.53 (0.34, 0.82)	-	0.44 (0.33, 0.60)	-
	P value vs. Placebo	0.004	-	< 0.001	-

		TEZ-IVA Study 106		Orkambi TRAFFIC & TRANSPORT studies	
Number of pulmonary exacerbations requiring i.v. antibiotic and/or hospitalization through Week 24	**Rate Ratio vs. Orkambi, 95% CI**	[redacted]	-	-	-
	P value vs. Orkambi	[redacted]	-	-	-
Absolute change in BMI from baseline at Week 24 (kg/m2)	Mean (SD) at Baseline	20.96 (2.95)	21.12 (2.88)	21.50 (3.03)	21.02 (2.92)
	LS Mean (SE)	0.18 (0.05)	0.12 (0.05)	0.37 (0.05)	0.13 (0.05)
	P value within treatment	<0.001	0.013	<0.001	0.007
	LS Mean difference vs. placebo (SE) (95% CI)	0.06 (0.07) (-0.08, 0.19)	-	0.24 (0.07) (0.11, 0.37)	-
	P value vs. placebo	0.413	-	<0.001	-
	LS Mean difference vs. Orkambi, 95% CI	[redacted]	- -	- -	- -
	P value vs. Orkambi	[redacted]	-		-

For adverse events, a side-by-side comparison was conducted where the LUM/IVA arm included patients in the TRAFFIC and TRANSPORT studies who received either LUM/IVA 400/250 mg twice daily (every 12h) (i.e. the approved dose) or LUM 600 mg daily/IVA 250 mg every 12h (currently not approved). The overall AE rates were similar between TEZ/IVA, LUM/IVA, and placebo (>90%). A higher proportion of patients on LUM/IVA or placebo in the pooled TRAFFIC and TRANSPORT studies experienced treatment related AEs (48% and 34.9%, respectively, vs 25.5% for TEZ/IVA and 25.6% for placebo in the EVOLVE study) and Severe Adverse Events (SAEs) (20.1% and 28.6% vs 12.4% for TEZ/IVA and 18.2% for placebo in the EVOLVE study). TEZ/IVA appears to have lower rates of discontinuation due to AEs than LUM/IVA (2.8% for TEZ/IVA and 3.1% for placebo in the EVOLVE study vs 4.2% for LUM/IVA and 1.6% for placebo in the TRAFFIC/TRANSPORT study). Norwegian clinicians told NoMA that the adverse event profile for TEZ/IVA is better than for LUM/IVA. Bronchial obstruction ("asthmatic reaction") is an important adverse event in patients with poor lung function. In these patients, TEZ/IVA will be an important alternative to LUM/IVA. In addition, TEZ/IVA will provide an option for patients receiving tuberculostatics and hormonal anticonception due to the interaction of LUM/IVA with those medications.

NoMA's assessment

LUM/IVA has not been previously assessed in terms of cost-effectiveness in the Norwegian setting and hence cannot be used as the main comparator for TEZ/IVA. Nevertheless, the company has submitted an ITC of TEZ/IVA vs LUM/IVA in terms of key efficacy outcomes and a side-by-side comparison of AEs.

The EVOLVE and TRAFFIC/TRANSPORT studies are very similar in terms of design and inclusion criteria (22, 23). Patient characteristics are aligned across the trials in terms of sex, age ppFEV1 at baseline and mean BMI. The trials are sufficiently similar to be indirectly compared via Bucher's method.

The results show that there is a significant difference between TEZ/IVA and LUM/IVA in terms of absolute change in ppFEV1 [redacted] at week 24. A comparison of the primary endpoint in EVOLVE, absolute change in ppFEV1 through week 24, was not conducted as this was not an endpoint in TRAFFIC or TRANSPORT. A change through week 24 is considered a more comprehensive measure of effect as all assessments over 24 weeks are incorporated while on treatment as opposed to only one assessment at arbitrary week 24. EMA has evaluated and commented on this comparison and stated that "*the difference of [redacted] in FEV1 is difficult to interpret from a point of clinical relevance. This is because the available literature describes that yearly decline in ppFEV1 levels are influenced by a number of factors, including age cohort and clinical factors such as pancreatic insufficiency, baseline FEV1, exacerbation, and Pseudomonas aeruginosa infection/colonization among others, and there is no consensus regarding a minimally clinically relevant difference in FEV1 decline for clinical trials and more in general therapeutic response purposes*" (24).

The superior effect of TEZ/IVA in the ppFEV1 measure was not supported by the secondary endpoints such as the number of pulmonary exacerbations through Week 24, the number of pulmonary exacerbations requiring i.v. antibiotic and/or hospitalization through Week 24, absolute change in BMI from baseline at Week 24 or absolute change in CFQ-R Respiratory Domain Score from baseline at Week 24.

EMA has also evaluated data from Study 114 which was a phase 3b, randomized, double-blind, placebo-controlled, parallel-group trial to assess the safety and efficacy of TEZ/IVA in patients who had to discontinue LUM/IVA due to respiratory side effects such as chest discomfort, dyspnea, and respiration abnormal (chest tightness). This study confirms that TEZ/IVA appears to be better tolerated than LUM/IVA, with comparable effect (24). Norwegian clinicians support this evaluation.

Overall, TEZ/IVA (Symkevi) is considered similar to LUM/IVA (Orkambi) in terms of efficacy.

3 PICO[3]

3.1 Patient Population and Best Supportive Care

Norwegian clinical practice

Approximately 350-375 patients are living with CF in Norway - and over 300 CF patients are included in the Norwegian CF Medical Quality Registry (*Nasjonalt medisinsk kvalitetsregister for cystisk fibrose*), and data from these patients was included in the Annual Report for 2017 (5). The description of patient characteristics from the Norwegian Registry is provided further down in this chapter, please see under the heading "NoMA's assessment".

[3] Patients, Intervention, Comparator, Outcome.

Submitted clinical studies

The studies relevant to this STA are the EVOLVE study for F/F patients and the EXPAND study for F/RF patients. Key inclusion- and exclusion criteria for these studies are summarised in table 5, and baseline patient characteristics in Table 6.

Table 5 Key inclusion- and exclusion criteria in the EVOLVE and EXPAND studies (source Vertex)

EVOLVE	**EXPAND**
Key inclusion criteria	**Key inclusion criteria**
-Patients with a confirmed diagnosis of CF (defined as sweat chloride value ≥60 mmol/L) -Stable CF disease as judged by the investigator -Confirmed genotype of *F508del/F508del* -Age 12 years or older -FEV1 ≥40% and ≤90% of predicted normal for age, sex, and height (equations of Wang et al. or Hankinson et al., depending on age) during screening	-Patients with a confirmed diagnosis of CF -defined as sweat chloride value ≥60 mmol/L, or -based on documented sinopulmonary disease -Stable CF disease as judged by the investigator -Confirmation of F508del/RF genotype -Age 12 years or older -FEV1 ≥40% and ≤90% of predicted normal for age, sex, and height (equations of Wang et al. or Hankinson et al., depending on age) during screening
Key exclusion criteria	**Key exclusion criteria**
-A history of any comorbidity that may confound the results of the study or pose an additional risk in administering the study medication -Any clinically significant laboratory abnormalities that may interfere with the study assessments or pose an undue risk to the patient -An acute upper or lower respiratory tract infection, pulmonary exacerbation, or changes in medication (including antibiotics) for pulmonary disease in the 28 days before the first dose of study medication -Ongoing or prior participation in an investigational drug study (including studies investigating TEZ and/or IVA) within 30 days of screening -Participation in clinical studies of Orkambi or having taken Orkambi, whether physician-prescribed or through an early access program -Colonization with organisms associated with a more rapid decline in pulmonary status (e.g. *B. cenocepacia*, *B. dolosa*, and *Mycobacterium abscessus*)	-A history of any comorbidity that may confound the results of the study or pose an additional risk in administering the study medication -Any clinically significant laboratory abnormalities that may interfere with the study assessments or pose an undue risk to the patient -An acute upper or lower respiratory tract infection, pulmonary exacerbation, or changes in medication (including antibiotics) for pulmonary disease in the 28 days before the first dose of study medication -Ongoing or prior participation in an investigational drug study (including studies investigating TEZ, lumacaftor and/or IVA) or use of commercially available Kalydeco within 30 days of screening -Colonization with organisms associated with a more rapid decline in pulmonary status (e.g. *B. cenocepacia*, *B. dolosa*, and *Mycobacterium abscessus*)

Table 6 Baseline patient characteristics in EVOLVE (trial 106, F/F genotype) and EXPAND (trial 108, F/RF genotype)(8)

Characteristic	Study 106		Study 108 (Period 1)[c]		
	Placebo N = 256 n (%)	TEZ/IVA N = 248 n (%)	Placebo N = 80 n (%)	IVA N = 81 n (%)	TEZ/IVA N = 83 n (%)
Age at screening (years)					
Mean (min, max)	25.7 (12, 61)	26.9 (12, 64)	32.6 (12, 72)	36.3 (12, 69)	35.6 (12, 68)
Age groups at screening (years), n (%)					
<18	58 (22.7)	58 (23.4)	11 (13.8)	12 (14.8)	11 (13.3)
≥18	198 (77.3)	190 (76.6)	69 (86.3)	69 (85.2)	72 (86.7)
Sex, n (%)					
Male	131 (51.2)	127 (51.2)	34 (42.5)	41 (50.6)	35 (42.2)
Female	125 (48.8)	121 (48.8)	46 (57.5)	40 (49.4)	48 (57.8)
Region, n (%)					
North America	68 (26.6)	59 (23.8)	39 (48.8)	36 (44.4)	45 (54.2)
Europe[a]	188 (73.4)	189 (76.2)	41 (51.3)	45 (55.6)	38 (45.8)
Weight (kg)					
Mean (min, max)	58.9 (33.0, 107.0)	58.1 (29.0, 93.0)	69.7 (42.0, 112.0)	71.1 (40.0, 156.9)	67.7 (43.0, 127.0)
BMI (kg/m^2)[b]					
Mean (min, max)	21.12 (14.47, 32.24)	20.96 (13.67, 30.04)	24.56 (15.59, 36.99)	24.51 (15.19, 49.65)	23.61 (16.18, 42.43)
Residual function mutation, n (%)					
Non-canonical splice	NA	NA	48 (60.0)	48 (59.3)	50 (60.2)
Missense	NA	NA	32 (40.0)	33 (40.7)	33 (39.8)
$ppFEV_1$ at baseline					
Mean (min, max)	60.4 (27.8, 96.2)	59.6 (30.3, 91.1)	62.1 (35.1, 93.5)	62.8 (35.0, 92.2)	61.8 (34.6, 91.4)
$ppFEV_1$ categories at baseline, n (%)					
<40	24 (9.4)	23 (9.3)	6 (7.5)	8 (9.9)	8 (9.6)
≥40 to <70	152 (59.4)	157 (63.3)	48 (60.0)	46 (56.8)	48 (57.8)
≥70 to ≤90	73 (28.5)	65 (26.2)	25 (31.3)	26 (32.1)	25 (30.1)
>90	7 (2.7)	2 (0.8)	1 (1.3)	1 (1.2)	2 (2.4)
Missing	0	1 (0.4)	NA	NA	NA
Sweat chloride at baseline (mmol/L)					
Mean (min, max)	100.5 (42.0, 125.5)	101.3 (38.5, 140.0)	70.7 (19.0, 135.0)	74.9 (11.0, 112.5)	64.1 (12.5, 119.0)

CFQ-R Respiratory at baseline					
Mean (min, max)	69.9 (16.7, 100.0)	70.1 (6.7, 100.0)	67.8 (16.7, 94.4)	70.0 (16.7, 100.0)	66.5 (16.7, 100.0)
Colonization of *Pseudomonas aeruginosa*, n (%)					
Positive	182 (71.1)	185 (74.6)	48 (60.0)	45 (55.6)	52 (62.7)
Use of dornase alfa[c], n (%)	185 (72.3)	165 (66.5)	54 (67.5)	49 (60.5)	47 (56.6)
Use of azithromycin[c], n (%)	141 (55.1)	135 (54.4)	38 (47.5)	31 (38.3)	32 (38.6)
Use of inhaled antibiotic[c], n (%)	160 (62.5)	136 (54.8)	23 (28.8)	27 (33.3)	26 (31.3)
Use of bronchodilator[c], n (%)	234 (91.4)	222 (89.5)	71 (88.8)	68 (84.0)	74 (89.2)
Use of inhaled bronchodilator[c], n (%)	234 (91.4)	221 (89.1)	71 (88.8)	67 (82.7)	74 (89.2)
Use of inhaled hypertonic saline[c], n (%)	133 (52.0)	126 (50.8)	39 (48.8)	36 (44.4)	43 (51.8)
Use of inhaled corticosteroids[c], n (%)	162 (63.3)	139 (56.0)	45 (56.3)	48 (59.3)	50 (60.2)
Pancreatic insufficient[d], n (%)					
Yes	NA	NA	11 (13.8)	11 (13.6)	11 (13.3)

Sources: Study 106 CSR/Table 14.1.3 and Table 14.1.4; Study 108 CSR/Table 14.1.3 and Table 14.1.4

AE: adverse event; BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire-Revised; IVA: ivacaftor; n: number of subjects; FEV_1: forced expiratory volume in 1 second; SD: standard deviation; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in the study.

[a] For Study 106 Europe includes Switzerland. For Study 108, subjects in Israel and Australia have been presented under Europe.

[b] BMI = Weight/(Height × Height) kg/m^2.

[c] Includes medications started before the first dose of study drug in the study and continuing during the treatment period.

[d] Fecal elastase-1 <200 µg/g. Fecal elastase was not collected in Study 106 because F/F subjects are expected to be pancreatic insufficient.

[e] Data from Study 108 Treatment Period 1 were presented to represent the baseline characteristics of the study population. No meaningful differences were observed in Treatment Period 1 and 2 for any treatment group.

In the crossover study EXPAND, baseline characteristics and within-subject differences were comparable between treatment period 1 and 2 (not shown).

Submitted health economic analyses

Vertex has submitted two health economic models; one for the F/F genotype and one for the F/RF genotype group. In the models, data from the UK CF Registry (UKCFR) Annual Report for 2008 (19) are used in addition to the results from the EXPAND study for the F/RF genotype, and the EVOLVE, TRAFFIC and TRANSPORT (TT) studies for the F/F genotype. The 2008 UK CFR Annual Report is based on 6,082 patients (who received BSC) grouped into birth cohorts ranging from 1980 to 2008 (19). The UK Registry is mainly used to provide information on the predicted overall survival of the patients. For the F/F genotype, two options for the patient pool are available; patient characteristics from the EVOLVE and TT studies, or the EVOLVE study only. For the F/RF genotype, patient characteristics patient characteristics from the EXPAND study is available.

Table 7 Baseline characteristics for the cohort of sampled patients with F/F genotype at baseline from EVOLVE only and in the model ((8) and Vertex)

Selected characteristics F/F patients		EVOLVE (study 106)		Modelled F/F cohort
		Placebo	TEZ/IVA	
Age	Age at screening (mean years)	25,7	26,9	26,8
Sex	Sex (% male)	51,2	51,2	52,7
Weigth	Weight (mean kg)	58,9	58,1	N/A
	BMI, kg/m^2 (mean)	21,12	20,96	N/A
	Weigth-for-Age Z-Score (mean)	N/A	N/A	-0,5
Lung function	ppFEV1 at base line (mean)	60,4	59,6	60,3
	Annual PEx rate (mean)	N/A	N/A	0,9
Sweat Chloride	Sweat Chloride at base line, mmol/L (mean)	100,5	101,3	N/A
HRQoL	CFQ-R Respiratory at base line (mean)	69,9	70,1	N/A
Colonization of pathogens	Colonization of P. aeruginosa (% positive)	71,1	74,6	N/A
	Colonization of B. cepacia (% positive)	N/A	N/A	2,1
	Colonization of S. aureus (% positive)	N/A	N/A	42,3
Pancreatic function	Pancreatic insuffieciency (% yes)	98	98	100
	Diabetes (% yes)	N/A	N/A	15,0

Table 8 Baseline characteristics for the cohort of sampled patients with F/RF genotype at baseline from EXPAND and in the model ((8) and Vertex)

Selected characteristics F/RF patients		EXPAND (study 108)		Modelled F/RF cohort
		Placebo	TEZ/IVA	
Age	Age at screening (mean years)	32,6	35,6	35,6
Sex	Sex (% male)	42,5	42,2	44,6

Weigth	Weight (mean kg)	69,7	67,7	N/A
	BMI, kg/m^2 (mean)	24,56	23,61	N/A
	Weigth-for-Age Z-Score (mean)	N/A	N/A	0,4
Lung function	ppFEV1 at base line (mean)	62,1	61,8	61,9
	Annual PEx rate (mean)	N/A	N/A	0,8
Sweat Chloride	Sweat Chloride at base line, mmol/L (mean)	70,7	64,1	N/A
HRQoL	CFQ-R Respiratory at base line (mean)	67,8	66,5	N/A
Colonization of pathogens	Colonization of P. aeruginosa (% positive)	60,0	62,7	N/A
	Colonization of B. cepacia (% positive)	N/A	N/A	2,1
	Colonization of S. aureus (% positive)	N/A	N/A	41,5
Pancreatic function	Pancreatic insufficiency* (% yes)	14	14	19,5
	Diabetes (% yes)	N/A	N/A	17,2

*Data for pancreatic insufficiency was missing for 14% of the F/RF patients from the EXPAND study, and confirmed insufficient for 14% of the patients.The majority (77%) of the patients were evaluated to have a sufficient pancreatic function (25).

NoMA´s assessment

The Norwegian CF Registry started to report Overall Survival as a part of the European CF Registry in 2016, and is therefore insufficient in order to provide robust survival curves that could be used in the model. The UK Registry is built on data from birth cohorts from 1980 to 2008 (19). During that period, CFTR modulators had not yet been introduced. Data for benchmarking between Norway and UK exist. Norway overall seems to have better outcomes than UK (6).

The use of external data to create a reference curve for survival prediction can be viewed in itself as a shortcoming. NoMA has several concerns regarding whether the patient population in the UK Registry matches the specific patient population eligible for TEZ/IVA in Norway:

1. The total UK CF population (all genotypes) is used as the basis of the survival curve, not only the patients with the specific F/F and F/RF mutations.
2. Incidence of different CF mutations varies between Norway and UK.
3. Age and incidence of phenotypes in the UK Registry, the EVOLVE and EXPAND studies and the Norwegian population are different.

4. Early diagnosis, BSC and prognosis have improved in the recent years, and a model based on older practice may not provide plausible estimates.

NoMA wishes to highlight several aspects that make the use of data from the UK CF Registry problematic as evidence for in the Norwegian CF population.

Overall UK CF population utilised to create a reference survival curve

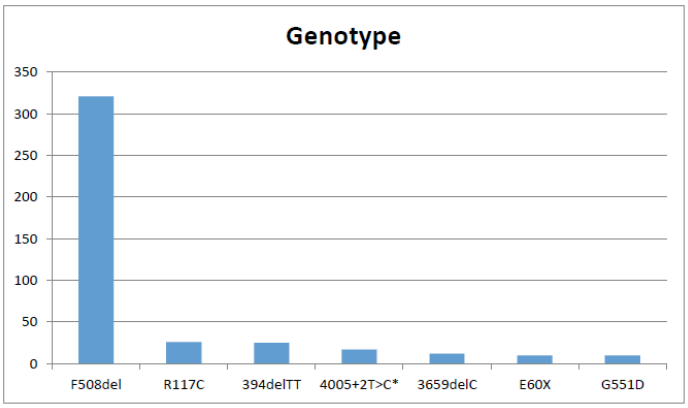
Norwegian CF clinicians highlight that there are large prognostic differences between classes of genotypes, but also *between* patients with same genotypes, due to patients' differing phenotypical expressions. According to a study by McKone and colleagues, CFTR genotype class I-III is associated with significantly reduced survival compared to class IV-V that could not be fully explained by differences in phenotypes (26). This suggests that CFTR mutations are independent predictors of survival, with causal effect on the patients' symptoms (i.e. phenotypical expression). Thus, the use of overall UK CF patient population may not reflect the relevant Norwegian subpopulations eligible to TEZ/IVA indication. Norway has the oldest CF population in Europe (6). According to Vertex, only aggregated OS KM-data for the whole UK CF-population are available.

NoMA considers the use of OS data for UK CF patients with all genotypes to be a major weakness when estimating survival for Norwegian patients with specific F/F and F/RF mutations in the model. This is further described throughout the report.

Norwegian total CF-population 2016 vs. UK total CF-population 2008, genotype:

Data from the Norwegian (2017) vs UK (2008) registries show that there were respectively 42% vs 54.3% CF patients with the F/F genotype in the populations (5, 19). The F/F genotype is, as previously noted, associated with severe disease on a group level.

Norwegian CF clinicians highlight that the Norwegian CF populations have a different distribution of genotypes than UK and other countries, and that there also exists some "local" mutations specific to some areas in Norway, for instance, the "Bergen mutation" 4005+2T>C. Figure 4 summarises which specific mutations are most frequent in the Norwegian and the UK registries.



*Bergensmutasjonen

All mutations; n(%)		
DF508	5244	(92.0%)
G551D	318	(5.6%)
G542X	190	(3.3%)
R117H	184	(3.2%)
621+1G->T	156	(2.7%)
1898+1G->A	77	(1.4%)

Figure 4 Number of alleles with at least one copy of the most frequent mutations. Left: Norwegian CF Registry 2017 (5). Right: UK CF Registry 2008 (19).

NoMA considers the UK data as robust as data based on 6 082 patients were included in the UK CF registry 2008 (19). The discrepancy between the reported proportions of F/F mutational status (42% vs 54.3%) undermines the representativeness of the UK reference survival curve to the Norwegian setting.

Age and incidence of phenotypical characteristics:

For the F/F population an option of including patient characteristics from the LUM/IVA studies TRAFFIC and TRANSPORT (TT) is available in the model. Vertex is using this option as their base-case population in order to expand the patient pool. However, as LUM/IVA is not used as a treatment option in the F/F model, NoMA has chosen to use patient characteristics from the EVOLVE study only, as study results are observed in this populations.

Changing the base-case population from the "EVOLVE + TT" study to "EVOLVE" study changes modelled long-term effect estimates in *both* the TEZ/IVA arm and the BSC arm in the model. This is probably due to the characteristicas prognostic effect, changing patient charactersics for the cohort will also alter the cohorts effect estimates. NoMA has not looked further into the altered results by this change.

The TEZ/IVA trials included patients ≥12 years. The *mean* age in the modelled cohorts was 26.8 years for F/F patients and 35.6 years for F/RF patients (the cohorts also included patients ≥12 years). The mean age in the Norwegian Registry for F/F and F/RF patients ≥12 years was higher than in the TEZ/IVA trials with respective 30.1 years and 56.5 years (Table 9). According to clinicians, Norwegian CF patients receive very good BSC which may positively affect prognosis. This is also reflected through benchmark parameters compared to other European countries (6).

Table 9 Age for Norwegian CF patients, collected from the Norwegian CF registry May 2019(27)

	Mean age (median) (patients >12 years)	Mean age (median) (patients >18 years)	Average age (median) (All patients independent of age)
Homozygote F/F	30,1 (29)	32,9 (30,5)	24,7 (24)*
Heterozygote F/RF	56,5 (42)	46,0 (42)	42,6 (32,5)
All patients	35,7 (30)	38,9 (36)	28,6 (24,5)

*3 patients registered as dead in 2018, aged 32, 33 and 34 years were not included in this statistic.

As previously explained, the abbreviation F/RF in the EXPAND study includes 14 specific RF mutations, and F/RF is defined in a broader way (all mutations considered to code for residual function are included) in the Norwegian Registry which may explain the large gap between the study and the registry. Norwegian data for the 14 specific RF mutations were not available. NoMA accepts that the mean age for patients >12 years old from the EXPAND trial is applied as the starting age in the F/RF model (median age not reported). For the F/RF patients, NoMA considers data from the EXPAND study to be the best available estimate.

For the F/F population, this genotype is defined the same way in the study and the registry. The mean age of Norwegian F/F patients is about 3 years higher than in the EVOLVE study. For the F/F population NoMA has used age from the Norwegian Registry and not the EVOLVE study when calculating absolute shortfall, as the registry gives the best estimate for Norwegian clinical practice. It is not possible to change the mean age parameter in the models when calculating ICER, this can only be done when calculating absolute shortfall.

The models are based on an assumption that certain patient characteristics (phenotypical expressions) are correlated with prognosis, and only those characteristics assumed to be of importance for survival are included in the model. Table 8 and 9 above shows baseline characteristics from EVOLVE and EXPAND studies and in the models.

The models do not consider baseline levels for sweat chloride or incidence of *Pseudomonas aeruginosa* infections, even though these were reported in the trials. Furthermore, the patient pools in the models are assigned some characteristics that were not reported in the trials: infections with microorganisms *B. capecia* and *S. aureus*, pancreatic suffiency (F/F), diabetes, and mean annual PEx rate. Estimates for those parameters in the models were based on information from the Norwegian and UK registries, and clinical experts. According to EMA, there is lack of consensus on defining PEx (4). PEx at baseline and as an endpoint in the TEZ/IVA studies were defined in the same way.

According to Norwegian clinicians the modelled baseline characteristics (Table 7, Table 8) are generally representable for Norwegian patients. However, the clinicians drew attention to some shortcomings that may influence the analysis.

Pseudomonas aeruginosa (PA) colonization is an important phenotypical characteristic as a chronic infection with PA often is considered the direct cause of death. The status of *chronic* lung infection due to PA was not collected in the studies; from the EVOLVE study it was reported that 71.1% - 74,6% were positive for PA at baseline, and in the EXPAND study 60% - 62.7% were positive. Chronic infections with PA were more common in the UK total CF population (2008) than in the Norwegian total CF population (2017); the incidence for UK patients (children and adults) was 39.5%, compared to 6.7% (Norwegian children) and 34% (Norwegian adults) (5, 19). If the long-term incidence of chronic PA infections, or the time of onset of these infections, are affected by TEZ/IVA treatment, the baseline level of PA for the population may affect the survival curves. Unfortunately, the models are not set up to capture the effects related to chronic PA colonisation.

In the model more patients (17.2% vs 14.7%) have diabetes in the F/RF population with 19,5% pancreatic insufficiency compared to the F/F population where 100% of the patients are assumed to have pancreatic insufficiency. NoMA consider this not plausible. Insulin is produced in the pancreas, and therefore pancreatic functioning is strongly correlated to diabetes. Cystic fibrosis related diabetes ia a very rare type 1 diabetes according to clinicians. The Norwegian CF-Registry reports that 3/80 (3,8%) children ≤18 years and 28/150 (18.7%) adults in the total Norwegian CF population (all genotypes) were treated with insulin in 2016. In the models these proportions are applied for both F/F and F/RF patients, but since the mean age is lower in the F/F population, also the incidence of diabetes is lowered in the model. In the model, diabetes is directly linked to age and not the causal lack of pancreatic function (which again is linked to type of CFTR mutation). This illustrates some of the shortcomings of the model and the use of external data when describing the F/F and F/RF subpopulations. Data collected from the broad CF population consisting of all genotypes, cannot necessarily be applied to specific genotypes. NoMA has explored the impact of the incidence of diabetes in a sensitivity analysis (see chapter 4.2.3).

Lung function measured by FEV1 declines by age with a similar pattern recorded for both the Norwegian and UK CF patients. Figure 5 is based on the total CF population and shows that on a group level FEV1 increases at about 30-35 years of age, suggesting that patients with higher FEV1 remain alive. As median age is shorter with more severe genotypes, the increase in FEV1 may represent patients with altered distribution of genotypes on a group level. Differences in median age between genotypes and the inconsistent pattern for lung function by age show that aggregated data for all CF patients contribute to large uncertainties when specific genotypes are modelled.

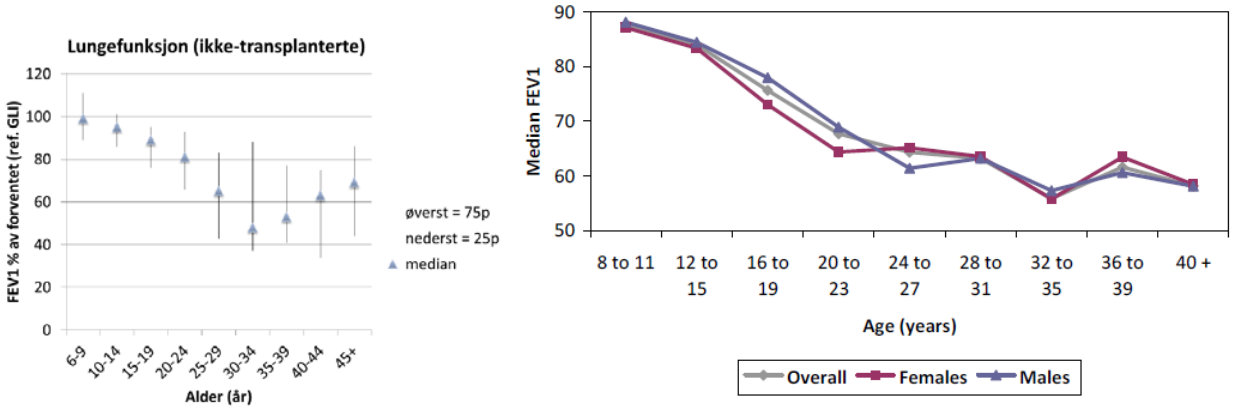


Figure 5 Lung function distributed by age. Left: Norwegian population (non-transplants) 2017 (5). Right: UK population 2008 (19)

In total NoMA considers it probable that Norwegian CF patients ≥12 years with specific F/F and F/RF mutations have prognoses that differ from the broad UK CF 2008 population (all ages and genotypes).

<u>BSC in Norway vs. other countries, and improved quality of BSC over the recent years:</u>

Outcome, prognosis and treatment of CF differed among European/Western countries in 2011 (2), and this may still be the case in 2019/2020. Some of the differences in prognosis can be explained by the fact that the most common genotypes differ between these countries (6). However, discrepancies in disease management and compliance to the BSC regimen are also likely to influence CF patient prognosis. There is general agreement that advice on treatment and management (BSC) is best provided by a multidisciplinary team at a CF centre, with care delivered by a team of professionals who spend much of their time treating CF patients (2). Such a centre exists in Norway.According to Norwegian clinicians, it is reasonable to expect that Norwegian clinical practice (BSC) at that time point was in accordance with the BSC that was offered in the clinical trials.

Since 2000, early European consensus guidelines have been published, a work that continues to develop (2). Both Norway and the UK have now adopted the European Guidelines. Newborn Screening (NBS) programmes for CF have been implemented since the early 1970s, but genetic testing has only been available since 1990. Presymptomatic detection permits early access to specialised medical care, and thus results in less morbidity and longer life expectancy. Good care provided at an early stage will minimise the short and medium effects of early pulmonary damage. In the absence of neonatal screening some infants will not be diagnosed until extensive irreparable damage to the lungs and/or other organs has occurred. Overall patients seem to be diagnosed at an early age in both Norway and the UK as both countries now have neonatal screening for CF (5, 19). The UK had started their NBS program in 2011 (2) while Norway according to clinicians started their program in april 2012, a small number of UK patients may have therefore started BSC at an earlier point than Norwegian patients.

As diagnostic technology has evolved since the 1980s, patients today may be diagnosed and treated at an earlier stage. This influences the overall survival of the patients that may not be captured in the models relying on survival data from 1980. While treatment patterns and diagnostics have developed, it is

complicated to find any comparator group with later births that will cover most of the life course of a person with CF.

Due to unavailability of more relevant sources, NoMA accepts that data from the UK CF registry is used to provide baseline patient characteristics and the reference survival curve in the model. This decision applies to this STA only, other considerations will be taken into account for other assessments.

A more thorough evaluation of the importance of model input parameters is presented further in chapter 3.3.1.

3.2 INTERVENTION

Norwegian clinical practice

Symkevi (TEZ/IVA) has not been used in Norwegian clinical practice, but other CFTR modulator regimens Kalydeco (IVA) monotherapy and Orkambi (LUM/IVA)) have been available; 15 and 30 patients respectively used these drugs in 2018. According to Norwegian clinicians, TEZ/IVA will be used according to the approved indication if it is reimbursed, that is for the specified genotypes. Tezacaftor 100 mg/ivacaftor 150 mg (morning) in combination with ivacaftor 100 mg (evening) will be added to BSC.

Based on information from the Norwegian CF registry and opinions from clinicians, 140 patients in Norway can potentially be treated with TEZ/IVA per year. This estimate includes 110 patients with F/F mutation (of which 40 patients are adults) and about 30 patients with F/RF mutations specified in the labeled indication for TEZ/IVA. NoMA expects patient numbers to be stable for the next five years.

According to Norwegian clinicians, treatment with TEZ/IVA, is considered relevant for both young patients (aiming to prevent early reversible damage caused by lowered/lacking CFTR function), as well as older patients with severely expressed CF (aiming to maintain the remaining organ function). Based on current knowledge about TEZ/IVA, Norwegian clinicians would like to treat all eligible patients.

Submitted health economic analyses

Modelling of effect in the TEZ/IVA arm is explained and evaluted in chapter 3.3.1.
Drug costs for TEZ/IVA morning dose and IVA evening dose are included in the model.
Vertex applied a compliance rate of 80% in the health economic models, as opposed close to 100% that was reported in the EVOLVE and EXPAND studies. The 80% compliance rate is derived from a retrospective cohort study with American data from Truven Health Market Scan Commercial Claims and Encounters Database (MSCCD), where the objective was to analyse the impact of IVA on the health resource utilization through analysis of claims data (28). Vertex assumes that compliance rates will be similar for all CFTR modulators. In the models, the compliance rate is assumed to only affect costs.

14.3% and 8.1% of the patients discontinue treatment after 24 and 8 weeks in the models (e.g. duration of the EVOLVE and EXPAND studies). After 24 and 8 weeks, it is assumed in both models that all patients will continue treatment with TEZ/IVA for as long as they live.

NoMA´s assessment

According to the EMA guideline on the clinical development of medicinal products for the treatment of CF and therapies aimed at improving CFTR function (4), the translation of disease improvement into improved organ function may be limited by the level of irreversible damage at the time of treatment initiation. Based on this, it is expected that the greatest benefit of such therapy may be children younger than 12 years, but as this STA is based on the labeled indication for patients ≥12 years, and since data in the health economic model is based on the EVOLVE and EXPAND studies which only included patients ≥12 years, NoMA has not assessed the therapeutic value or cost-effectiveness of initiating the therapy in a younger population.

The compliance rate from the TEZ/IVA trials was nearly 100%, but Vertex assumes that this will be lower in clinical practice. Vertex assumes that compliance will be similar for different CFTR modulators, and applied a compliance rate of 80% for the post trial period in the models. This rate is calculated from a retrospective cohort study, MSCCD (28). In the MSCCD cohort, administrative claims data from 79 commercially insured CF patients ≥6 years receiving IVA in the US were used. A medication possession ratio (MPR) was estimated, dividing total days of IVA supply with 365 days. NoMA does not have information on whether permanent discontinuation is accounted for in the MPR calculations. The average MPR in the cohort study was 0.8 (SD=0.3). Patients with single-month supply claims (n=63) had an average MPR of 0.8 (SD=0.3), while those with multi-month claims (n=16) had an average MPR of 0.9 (SD=0.2).

The Norwegian Prescription Database (NorPD) (17) provides data about dispensed drugs in Norway, which is drugs used in a home care setting. Respectively 13 and 15 patients used IVA (monotherapy) in years 2017 and 2018, while 28 and 30 patients used LUM/IVA. NoMA has calculated an average MPR for 2017 and 2018 based on the number of users (all ages) and turnover by dosage. An average MPR of 0.76-0.79 were calculated for IVA, and an average MPR of 0.62-0.76 were calculated for LUM/IVA. NorPD does not include drugs used by hospitalised patients, and MPR rates might be higher than the calculated rates. Similar to the MSCCD cohort trial, the NorPD search does not provide any information regarding permanent discontinuations.

Given the similar safety profiles for IVA monotherapy and TEZ/IVA, NoMA agrees that an MPR for IVA monotherapy and TEZ/IVA may be similar. Data from NorPD supports the estimated rates used in the model. However, since this estimate is uncertain, NoMA has tested the sensitivity of MPR in terms of ICER results. As drug costs affect the ICER results to a very large extent, the model is very sensitive to changes in the applied MPR.

In the models, the MPR is a proxy for compliance rate, but this only affects drug costs. The model does not take into account that non-compliance can impact on treatment outcomes. This is a very strong and

uncertain assumption, but as it is not known to what extent the MPR can affect the treatment outcomes, NoMA has not been able to account for this.

Efficacy results in the EVOLVE and EXPAND studies are based on a TEZ/IVA compliance rate close to 100%. Relative effect after week 24 and week 8 (i.e. duration of the EVOLVE and EXPAND studies) is based on results from populations with a 100% compliance rate in the health economic model, while costs for TEZ/IVA in the model correspond to a 80% compliance rate.
NoMA accepts this compliance rate for costs in lack of a better estimate. The sensitivity of altering the compliance rate is shown in section 4.2.2

Duration of TEZ/IVA therapy:

In the models 14.3% (F/F population) and 8.1% (F/RF population) of the patients discontinue treatment after 24 and 8 weeks (e.g. duration of the EVOLVE and EXPAND studies). During the 96 week follow-up in Study 110, 107 (13.5%) of the 789 included patients with F/F and F/RF genotype discontinued TEZ/IVA. The majority of these patients (685/789) were included from EVOLVE and EXPAND, and the rest of these patients were included from other TEZ/IVA studies for F/F patients.

22nd of October 2019 Vertex submitted final follow up data from Study 110.

NoMA applies a discontinuation rate corresponding to EVOLVE, EXPAND and study 110. See also chapter 3.3.1 for further discussions on duration of treatment.

3.3 OUTCOMES

3.3.1 Efficacy

Submitted clinical studies

The EVOLVE study enrolled patients between January 30th 2015 and January 20th 2017. The EXPAND study enrolled patients between March 27th 2015 and February 16th 2017. Study 110 enrolled patients between August 31st 2015 and March 6th 2017. All studies are now completed.

In the 24-week EVOLVE study assessments were undertaken at each study visit, that is at baseline, day 15 and at week 4, 8, 12, 16 and 24, except for sweat chloride which was measured at week 4, 16 and 24 (22). The primary endpoint was the absolute change in ppFEV1 from baseline through week 24. Secondary endpoints were change from baseline and week 24 for ppFEV1 (relative change), number of exacerbations, BMI (absolute change), sweat chloride (absolute change), health-related quality of life (absolute change in CFQ-R) and safety.

The EXPAND study had similar design and endpoints, but TEZ/IVA treatment period was 8 weeks. In the EXPAND study the absolute change in ppFEV1 was calculated between baseline and the average of

measured values at week 4 and 8. Due to the shorter trial duration, number of exacerbations was defined as an explorative endpoint in the EXPAND study.

<u>EVOLVE study – patients with homozygous F508del mutation (F/F):</u>
The average ppFEV1 value at baseline was 60.0 ± 15.2% of the predicted value. After 24 weeks of treatment, the absolute change in ppFEV1 in the TEZ/IVA arm was 4.0 percentage-points (95 % CI, 3.1 - 4.8) compared to placebo, the relative change was 6.8% (95 % CI, 5.3% – 8.3%) in favour of the TEZ/IVA arm. The absolute and relative changes were statistically significant (8). The estimated rate of yearly exacerbations was also significantly lower in the TEZ/IVA arm (0.64 vs. 0.99 events). For changes in HRQoL measured by CFQ-R see chapter 3.3.3. Significant changes were not observed for BMI. The tables and figure below shows effect results from the EVOLVE study.

Table 10 Results from the EVOLVE trial (8)

Effect estimate per comparison	Primary endpoint	Comparison groups	TEZ/IVA versus placebo
		LS mean difference absolute change ppFEV1	4.0
		95% CI	3.1, 4.8
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	TEZ/IVA versus placebo
		LS mean difference relative change ppFEV1	6.8%
		95% CI	5.3, 8.3
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	TEZ/IVA versus placebo
		Rate reduction in PExs	0.65
		95% CI	0.48, 0.88
		P-value	0.0054
	Key secondary	Comparison groups	TEZ/IVA versus placebo
	endpoint	LS mean difference BMI	0.06
		95% CI	-0.08, 0.19
		P-value	0.4127
	Key secondary endpoint	Comparison groups	TEZ/IVA versus placebo
		LS mean difference CFQ-R (points)	5.1
		95% CI	3.2, 7.0
		P-value	N/A[a]
Notes	[a] The treatment difference for the LS mean absolute change from baseline in BMI was not statistically significant (P = 0.4127). Therefore, the hierarchical multiple testing procedure was stopped.		
Analysis description	**Secondary analysis** As other secondary efficacy endpoints, time-to-first pulmonary exacerbation, absolute change in sweat chloride from baseline, absolute change in BMI z-score from baseline (in subjects <20 years of age at time of screening) and absolute change in body weight from baseline were investigated. They all showed a positive effect for TEZ/IVA compared to placebo. **Ancillary analysis** The Forest Plot for the subgroups analysed, shows a consistent beneficial effect for TEZ/IVA compared to placebo. The lowest point estimate is 3.5 difference in the group of patients with low baseline FEV1 (ppFEV1 < 40%) and female sex.		

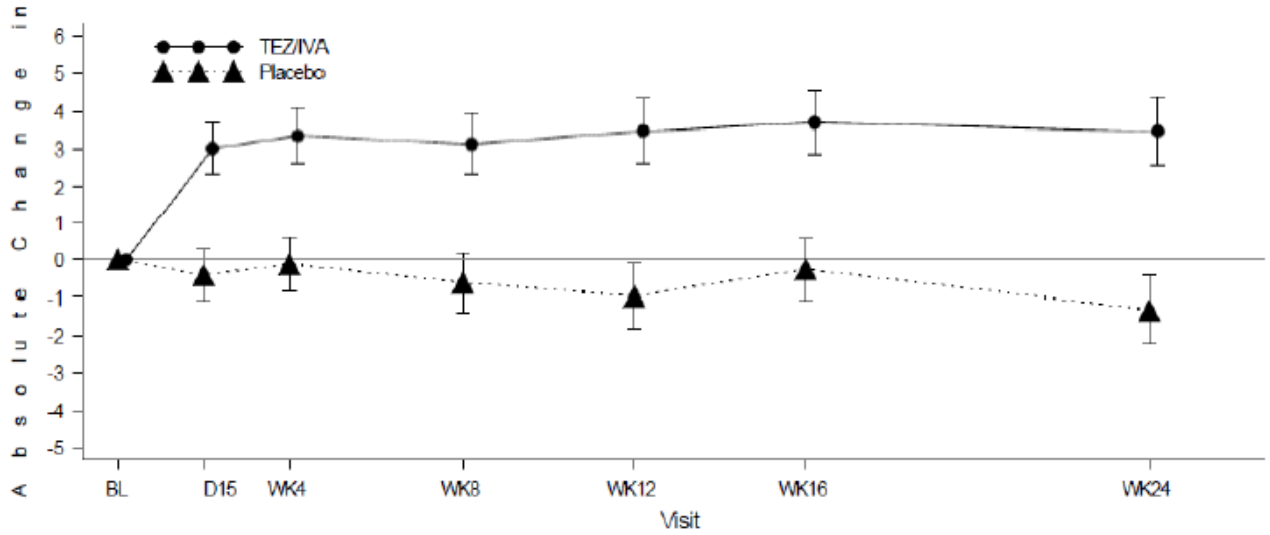


Figure 6 Plot over average changes in ppFEV1 up to week 24 in the EVOLVE trial (8)

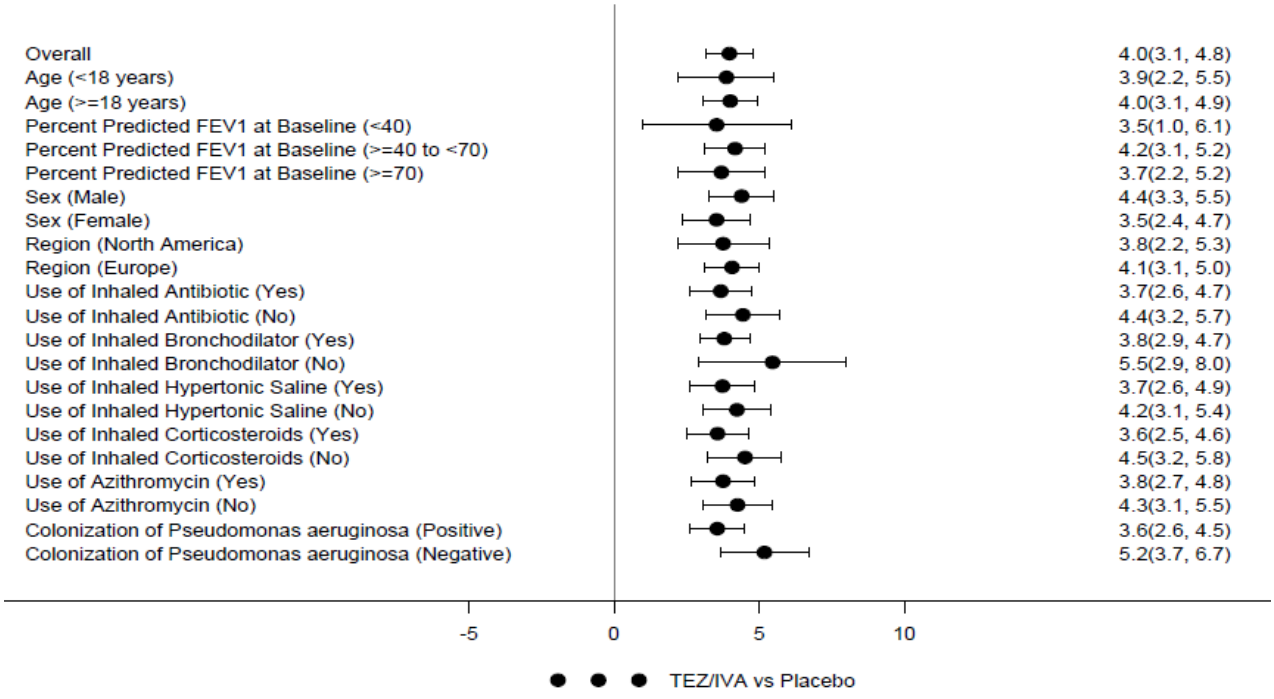


Figure 7 EVOLVE Forest Plot of LS Mean Difference between treatments with 95 % CI for Absolute Change From Baseline in Percent Predicted FEV1 through Week 24 by Subgroup Full Analysis Set (8)

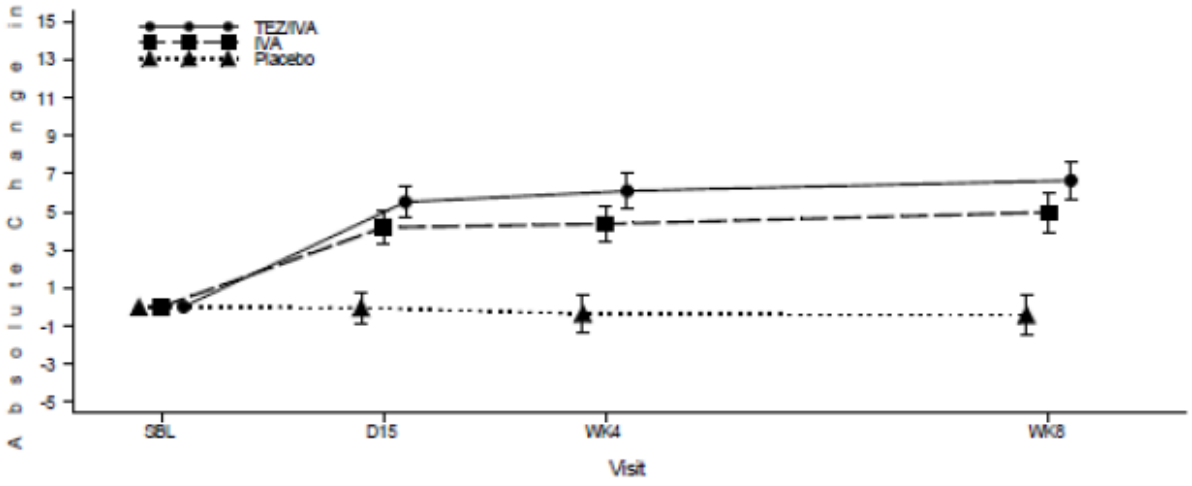
EXPAND study – patients with heterozygous F508del mutations (F/RF):

The average ppFEV1 value at baseline was 62.3 ± 14.5% of the predicted value. The LS mean treatment difference versus placebo for absolute change in ppFEV1 from study baseline to the average of Week 4 and Week 8 was 6.8 percentage points (95% CI: 5.7, 7.8; p<0.0001) for the TEZ/IVA group, and 4.7 percentage points (95% CI: 3.7, 5.8; p<0.0001) for the IVA group (8). The pulmonary exacerbations endpoint was exploratory and the results are descriptive only. The tables and figure below shows effect results from the EXPAND study.

Table 11 Results from the EXPAND trial (8)

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full analysis Set (FAS): all randomized subjects who carry the intended CFTR mutations and had received at least 1 dose of study drug. Week 4-8 per treatment period			
Descriptive statistics and estimate variability	Treatment group	placebo	ivacaftor	Tezacaftor/ivacaftor
	Number of subject	161	156	161
	LS mean change in ppFEV1	-0.3	4.4	6.5
	95% CI	-1.2, 06	3.5,5.3	5.6,7.3
	LS mean change in CFQ-R	-1	8.7	10.1
	95% CI	-2.9,1.0	6.8 10.7	8.2,12.1
Effect estimate per comparison	LS mean change in ppFEV1	Comparison groups	TEZ/IVA versus placebo	
		LS mean difference	6.8	
		95% CI	5.7, 7.8	
		P-value	<0.0001	
		Comparison groups	TEZ/IVA versus IVA	
		LS mean difference	2.1	
		95% CI	1.2, 2.9	
		P-value	<0.0001	
	LS mean change in CFQ-R	Comparison groups	TEZ/IVA versus placebo	
		LS mean difference	11.1	
		95% CI	8.7 13.6	
		P-value	<0.0001	
		Comparison groups	TEZ/IVA versus IVA	
		LS mean difference	1.4	
		95% CI	-1.0, 3.9	
		P-value	0.2578	
Notes				

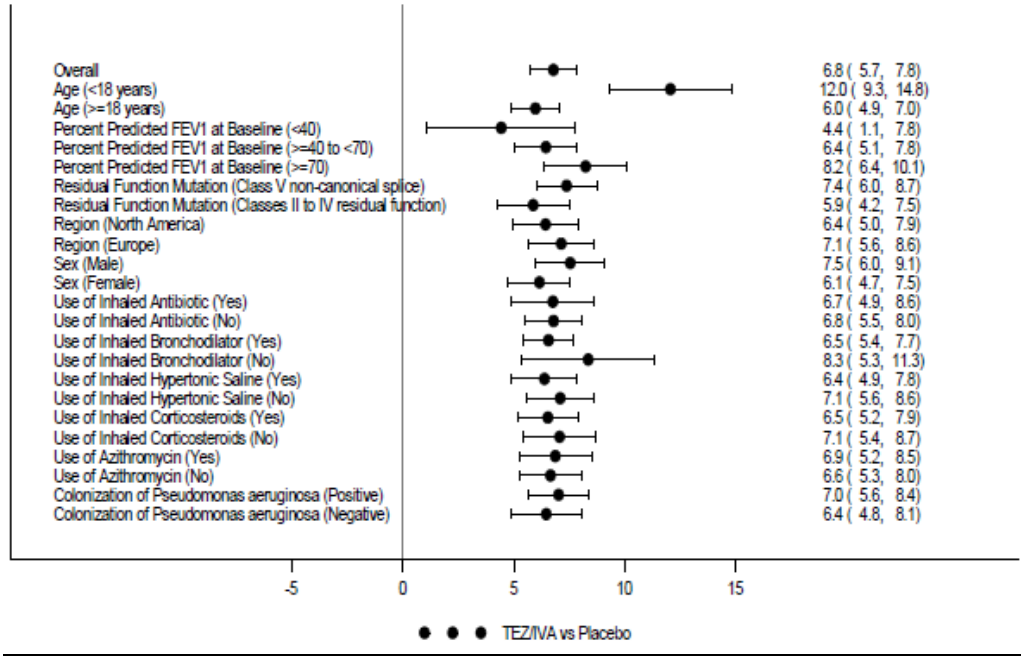
Analysis description	**Secondary analysis** As other secondary efficacy endpoints, relative Change in ppFEV1, absolute change in sweat chloride concentrations, additional Spirometry Variables, BMI and pulmonary exacerbations were measured. They all showed a positive effect for TEZ/IVA compared to placebo, while relative change in ppFEV1, sweat chloride and the additional spirometry variables showed a positive effect for TEZ/IVA compared to IVA. **Ancillary analyses:** The Forest Plot for the subgroups analysed, shows a consistent beneficial effect for TEZ/IVA compared to placebo. The lowest point estimate is 4.4 difference in the group of patients with low baseline FEV1 (ppFEV1 < 40%). The highest results are observed in the group of age < 18 years (12.0), FEV1 ≥70% or no use of bronchodilator (8.3). The number of patients per specific RF mutation is very small. Nevertheless the effects observed are supportive with the overall effects except for the deletions F508del/D110H and F508del/E831X.



Source: Figure 14.2.1.1
CI: confidence interval; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; IVA: ivacaftor; LS mean: least squares mean; MMRM: mixed-effect model repeated measures; TEZ: tezacaftor; UN: unstructured
Notes: Analysis included all measurements up to Week 8, both on-treatment measurements and measurements after treatment discontinuation. A UN covariance structure was used to model the within-subject errors. A Kenward-Roger approximation was used for the denominator degrees of freedom.

Figure 8 Absolute change in ppFEV1 from the EXPAND trial (8)

Table 12 Forest Plot of LS Mean Difference for Absolute Change From Study Baseline in ppFEV1 to Average of Week 4 and Week 8 by Subgroup, Full Analysis Set (8)



Open Label Extension follow-up Study 110:

Data submitted to NoMA 22nd of October 2019, with additional 96 weeks follow-up time (final cut off):

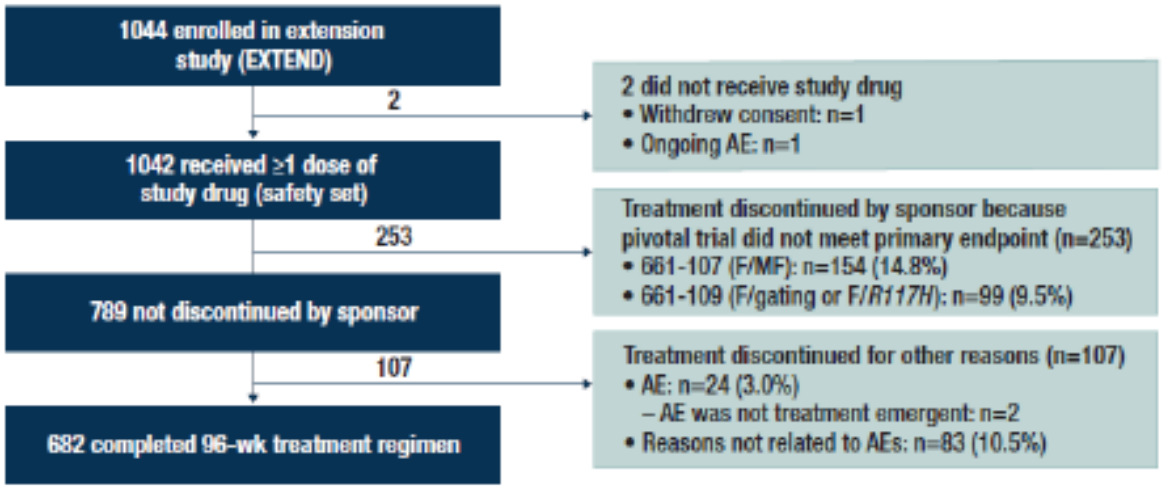


Figure 9 Patient Disposition Study 110 (Vertex)

In total 789 patients were included in Study 110, and 685 (86.4%) patients completed 96 weeks treatment – 459 F/F patients and 226 F/RF-patients.

ppFEV1:

EVOLVE study – patients with homozygous F508del mutation (F/F):
The average ppFEV1 value at baseline was 60.0 ± 15.2% of the predicted value. After 24 weeks of treatment, the absolute change in ppFEV1 in the TEZ/IVA arm was 3.4 percentage points (95 % CI, 2.7 - 4.0), and -0.6 percentage points (95 % CI, -1.3 - 0.0) in the placebo-arm compared to baseline. After additional 96 weeks of treatment in Study 110, the treatment effect compared to baseline was lowered and absolute change was reduced to 2.0 percentage points (95 % CI, 0.7 – 3.2). Results were similar for patients who received placebo in EVOLVE and crossed over to TEZ/IVA therapy in Study 110.

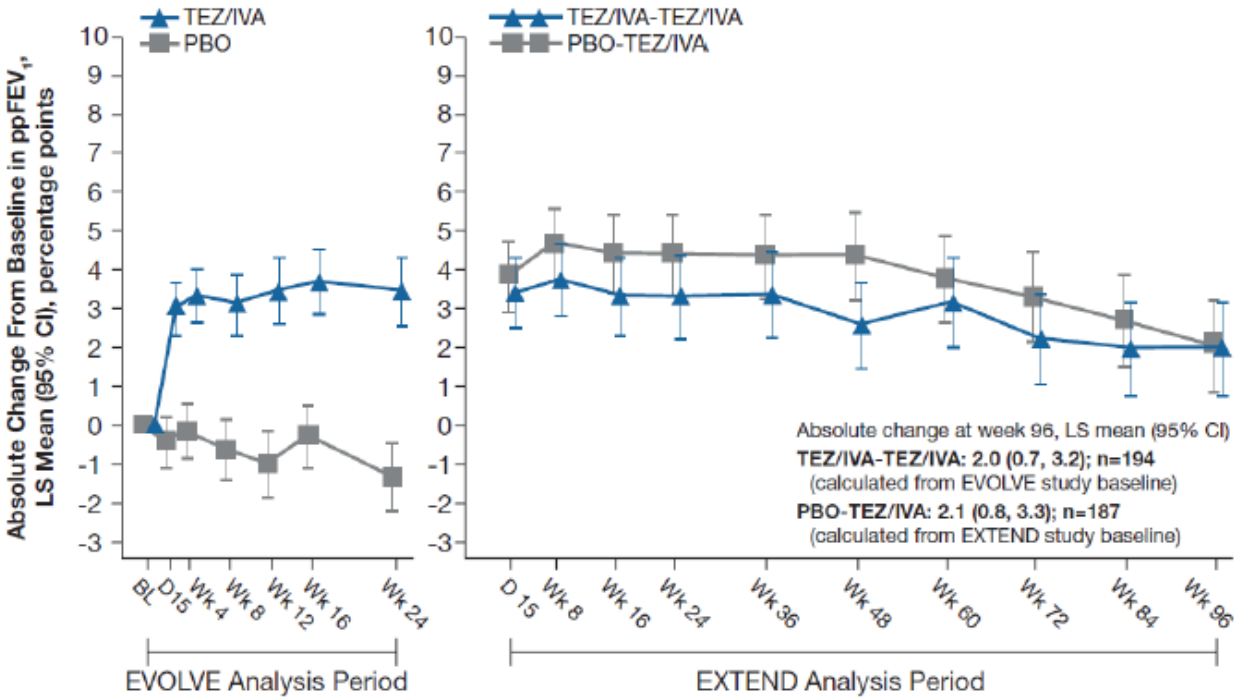


Figure 10 Absolute Change from Baseline in ppFEV1 in the 106/110 Efficacy Set (F/F) (Vertex)

<u>EXPAND study – patients with heterozygous F508del mutations (F/RF):</u>
The average ppFEV1 value at baseline was 62.3 ± 14.5% of the predicted value. The LS mean average absolute change in ppFEV1 at Week 4 and Week 8 was 6.5 percentage points (95% CI: 5.6, 7.3; p<0.0001) for the TEZ/IVA group and -0.3 percentage points (95% CI: -1.2, 0.6; p=0.50) for the placebo group compared to baseline.

The effect is maintained in the TEZ/IVA-group with additional 96 weeks of treatment in Study 110, absolute change was 7.5 percentage points (95 % CI, 5.6 – 9.4) compared to baseline in EXPAND. For patients who first received 8 weeks of placebo in the EXPAND study (the placebo-TEZ/IVA group), the absolute change compared to EXPAND baseline was 4.1 percentage points (95 % CI, 2.2 – 6.0) after receiving 96 weeks of TEZ/IVA treatment in Study 110.

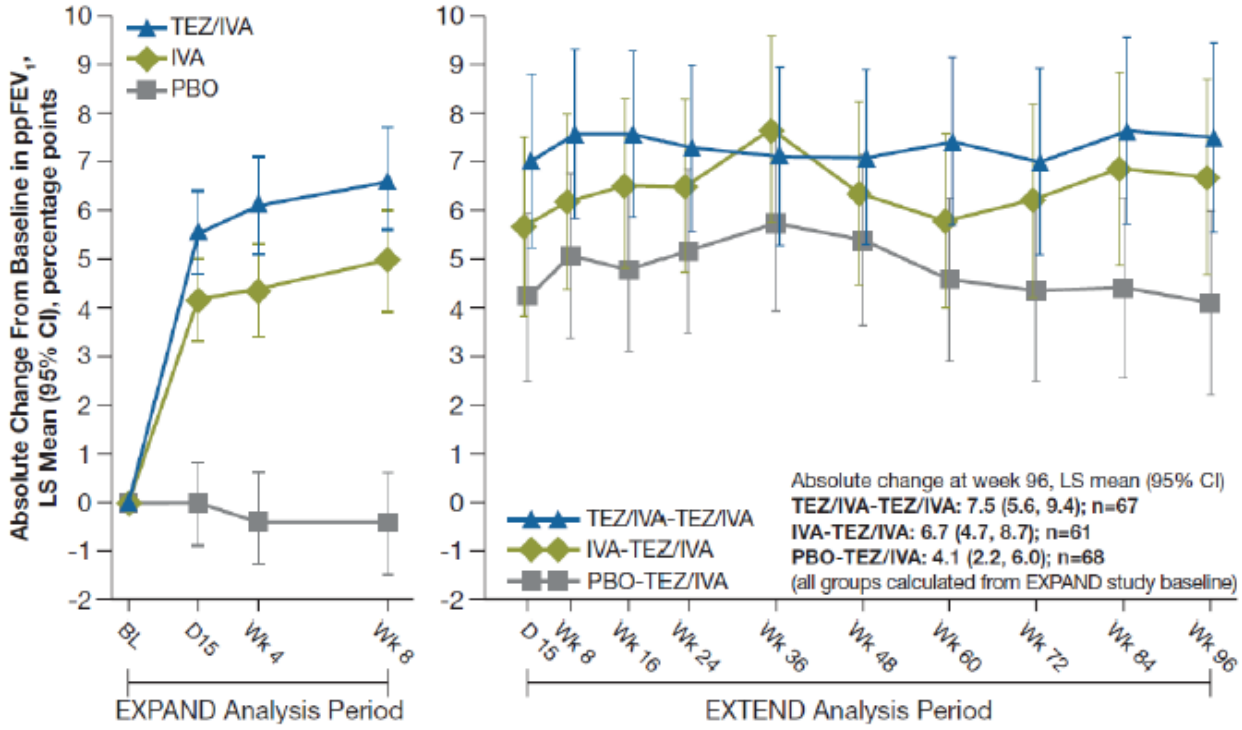


Figure 11 Absolute Change from Baseline in ppFEV1 in the 108/110 Efficacy Set (F/RF) (Vertex)

PEx:

Vertex has submitted updated annualized PEx rates calculations based on a year consisting of 48 weeks for the EVOLVE/110 and EXPAND/110 efficacy sets (Table 13 & Table 14).

Table 13 106/110 PEx Analysis Set (F/F) (Vertex)

	106/110 Efficacy Set		EVOLVE	
	PBO-TEZ/IVA (n=231)	TEZ/IVA-TEZ/IVA (n=248)	Placebo (n=256)	TEZ/IVA (n=248)
PEx				
Patients with events, n (%)	116 (50.2)	141 (56.9)	88 (34.4)	62 (25.0)
Total number of events	306	423	122	78
Estimated event rate per y (95% CI)	0.68 (0.55, 0.83)	0.76 (0.63, 0.92)	0.99	0.64
PEx requiring IV antibiotic				
Patients with events, n (%)	78 (33.8)	90 (36.3)	54 (21.1)	32 (12.9)
Total number of events	171	223	74	39
Estimated event rate per y (95% CI)	0.34 (0.25, 0.44)	0.36 (0.28, 0.47)	0.54	0.29
PEx requiring hospitalization				
Patients with events, n (%)	55 (23.8)	64 (25.8)	28 (10.9)	22 (8.9)
Total number of events	99	137	33	26
Estimated event rate per y (95% CI)	0.23 (0.16, 0.32)	0.24 (0.18, 0.32)	0.29	0.22

IV, intravenous; y, year.
[a] Annualized PEx rate was calculated based on 48 wks in a y.

Table 14 108/110 PEx Analysis Set (F/RF) (Vertex)

	108/110 Efficacy Set			EXPAND		
	PBO-TEZ/IVA (n=81)	IVA-TEZ/IVA (n=74)	TEZ/IVA-TEZ/IVA (n=78)	TEZ/IVA (N=161)[b]	IVA (N=156)[b]	PBO (N=161)[b]
PEx						
Patients with events, n (%)	40 (49.4)	36 (48.6)	28 (35.9)	11 (6.8)	9 (5.8)	19 (11.8)
Total number of events	89	51	46	11	9	20
Estimated event rate per y (95% CI)	0.44 (0.29, 0.66)	0.28 (0.18, 0.44)	0.22 (0.14, 0.35)	0.34	0.29	0.63
PEx requiring IV antibiotic						
Patients with events, n (%)	14 (17.3)	13 (17.6)	12 (15.4)	–	–	–
Total number of events	30	21	16			
Estimated event rate per y (95% CI)	0.09 (0.04, 0.22)	0.09 (0.04, 0.22)	0.05 (0.02, 0.13)			
PEx requiring hospitalization						
Patients with events, n (%)	12 (14.8)	11 (14.9)	9 (11.5)	–	–	–
Total number of events	16	17	11			
Estimated event rate per y (95% CI)	0.07 (0.03, 0.18)	0.09 (0.04, 0.22)	0.05 (0.02, 0.13)			

y, year.
[a] Annualized PEx rate was calculated based on 48 wks in a y.
[b] The number of patients in EXPAND is approximately twice as large as the number who rolled over into EXTEND due to the cross-over design of EXPAND.

Submitted health economic analyses

Initial base-case submitted by Vertex on 21-Dec-2018:

An individual patient state-transition model was built to estimate the incremental health outcomes and costs of TEZ/IVA versus BSC alone from a Norwegian healthcare perspective. At the start of the model, individual patient profiles are drawn from the pool of available patient profiles from the clinical studies. The patient profiles are then duplicated in order for the patients in each treatment assignment to be identical at model entry. This ensures the only difference between the cohorts is the treatment effect. The simulated patients are tracked through the model over time in discrete time-steps called cycles (see details in section 4.1).

Extrapolation of relative effect is based on published Kaplan-Meier (KM) curves of CF survival from the 2008 UKCFR annual report, which reported survival for 6,082 patients grouped into birth cohorts ranging from 1980 to 2008 (Cystic Fibrosis Foundation 2009). The published curves were digitized. Simulated patient-level (SPL) KM data were generated based on the digitized curve and the number of patients in each birth cohort using methods described in the literature (29, 30). Various parametric functions (exponential, Weibull, Gompertz, log-logistic, log-normal, and generalized gamma) were tested to arrive at the best parametric fit that is visually and statistically credible, as well as clinically plausible.

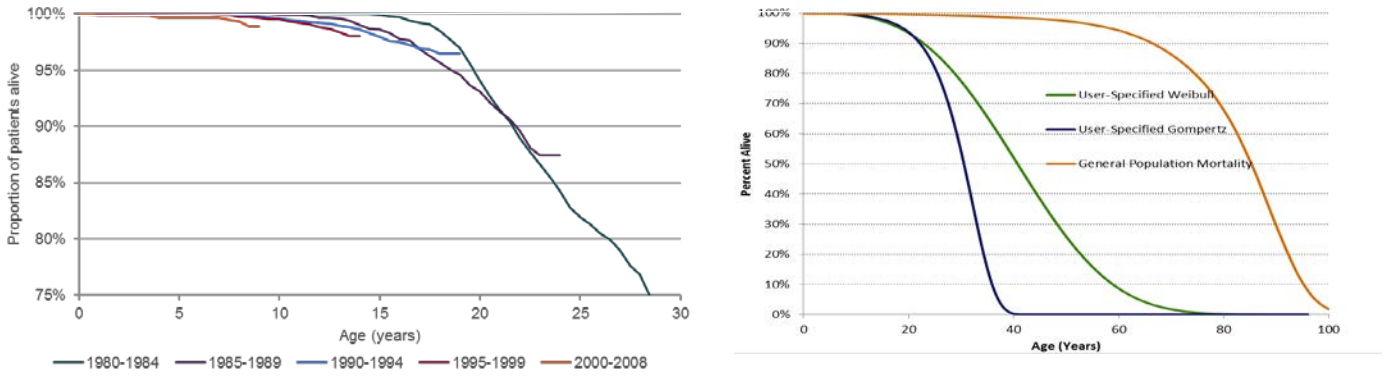


Figure 12 Kaplan-Meier curves of survival in the UK CF Registry birth cohorts (all genotypes) 1980-2008 (left), and parametrisation of the KM curves from the 1985–2008 birth cohorts (right).

In separate analyses of each birth cohort, median predicted survival estimates for the most recent birth cohorts were either clinically unrealistically high (e.g., more than 100 years) or unrealistically low (approximately 25 years), which is inconsistent with findings from similar analyses of other registry data (US Cystic Fibrosis Foundation 2011, Cystic Fibrosis Registry of Ireland 2013). Thus, final analyses were based on the 1985–2008 birth cohorts. The Weibull survival function was selected to be the best fitting parametric distribution, with a median predicted survival of 40.8 years (Figure 12).

To assess the mortality for an individual patient, the underlying hazard function fitted to the UKCFR population is modified to incorporate patient-level characteristics by using a Cox Proportional Hazard (CPH) model obtained from Liou et al (31). Liou et al developed the model based on data collected from 1993 to 1998 by the US Cystic Fibrosis Foundation Patient Registry (CFFPR) on 11,630 individuals aged 5.5 to 71.05 years and the following nine characteristics of patients with CF were found to predict survival: age, ppFEV1, sex, weight-for-age z-score, pancreatic sufficiency, diabetes, *S. aureus* infection, *B. cepacia* infection, and number of acute pulmonary exacerbations per year.

During each model cycle, patients' age, ppFEV1, weight-for-age z-score, the occurrence of pulmonary exacerbation, eligibility and occurrence of lung transplantation, development of diabetes, the occurrence of adverse events (AEs), and treatment discontinuation are updated. An overview of those parameters and the extrapolation assumptions is presented in Table 15. As patients move through the model, their probability of death is estimated at each cycle, conditioning on varying clinical characteristics.

Table 15 Efficacy input data used in the model

<table>
<tr><th>Parameter</th><th>Long-term extrapolation assumption</th><th>Value</th></tr>
<tr><td>Diabetes annual incidence rate</td><td>Age- and gender-stratified rate based on 8,029 patients from UK CF Registry during 1996-2005, ranging from 0–64 years of age, in which a total of 526 patients developed diabetes over a total follow-up of 15,010 person-years (32).</td><td>Annual Incidence Rate (per Person-year)
<table><tr><th colspan="2">Age Bound (Years)</th><th>Males</th><th>Females</th></tr><tr><th>Minimum</th><th>Maximum</th><th></th><th></th></tr><tr><td>12</td><td>19</td><td>0,039</td><td>0,060</td></tr><tr><td>20</td><td>29</td><td>0,049</td><td>0,071</td></tr><tr><td>30</td><td>39</td><td>0,065</td><td>0,072</td></tr><tr><td>40</td><td>100</td><td>0,051</td><td>0,029</td></tr></table></td></tr>
<tr><td>ppFEV1 annual change</td><td>EVOLVE/ EXPAND used for the trial period.

Natural decline over time assumed after the trial period.

BSC extrapolated annual decline based on US CFF Patient registry data (years 2006 to 2014) which were F/F and F/-RF population specific (33)

Treatment with TEZ-IVA+BSC in the F/F- population reduces the rate of decline by 42% based on data from a matched cohort analysis of LUM/IVA+BSC in this population (34). For the F/RF population, TEZ-IVA+BSC is assumed to reduce the rate of lung function decline by 47.1% based on a matched cohort analysis of IVA in G551D patients (35).</td><td>BSC Age dependent ppFEV1 annual change for predicted period
F/F population:
<table><tr><th>Min Age</th><th>Max Age</th><th>Change in $ppFEV_1$</th></tr><tr><td>6</td><td>12</td><td>-1,32</td></tr><tr><td>13</td><td>17</td><td>-2,37</td></tr><tr><td>18</td><td>24</td><td>-2,52</td></tr><tr><td>25</td><td>100</td><td>-1,86</td></tr></table>F/RF population:
<table><tr><th>Min Age</th><th>Max Age</th><th>Change in $ppFEV_1$</th></tr><tr><td>6</td><td>12</td><td>-0,80</td></tr><tr><td>13</td><td>17</td><td>-0,57</td></tr><tr><td>18</td><td>24</td><td>-1,85</td></tr><tr><td>25</td><td>100</td><td>-1,06</td></tr></table></td></tr>
<tr><td>Pulmonary Exacerbations (PEx) annual rate</td><td>For patients treated with BSC, an age-dependent exponential regression equation relating $ppFEV_1$ to the annual rate of pulmonary exacerbation is used. This relationship was obtained from 2004 US CFFPR data published by Goss et al (36) and was derived by Whiting et al (37) to relate patients' $ppFEV_1$ to their annual pulmonary exacerbation rate:
$$rate = ae^{-b \times ppFEV_1}$$</td><td>Two equations are applied: one for when patients are aged <18 years (a=8.594, b=0.035), and another for when patients are aged ≥18 years (a=3.789, b=0.026).

In F/RF the rate of PEx for TEZ-IVA+BSC was decreased by a rate ratio of 0.61 compared</td></tr>
</table>

	TEZ-IVA+BSC positively impacts both ppFEV1 and pulmonary exacerbations. These two clinical outcomes are interrelated, and the impact of TEZ-IVA+BSC on pulmonary exacerbations may be partially mediated through changes in ppFEV1. To adjust for the potential of double-counting treatment effects for ppFEV1 and pulmonary exacerbation, calibration techniques were used to derive a pulmonary exacerbation rate ratio for the CFTR modulator therapies relative to BSC that account for the impact of the acute improvement in ppFEV1.	to BSC for weeks 1-8 (38) and 0.55 for weeks 8+ (Model input calibrated to match 0.55 (25)). In F/F the rate of PEx for TEZ-IVA+BSC was decreased by a rate ratio of 0.55 compared to BSC for weeks 1-24 and weeks 24+ (calibrated to march RR of 0.53 (22)).
Weight-For-Age Z-Score	Weight-For-Age Z-Score is assumed to remain unchanged for BSC-treated patients for the entire model time horizon. For patients treated with a CFTR modulator, an absolute increase from baseline is applied by the end of the trial period, and no further changes for the remainder of the model.	0 for BSC 0 for TEZ-IVA+BSC as non-significant in the trial (F/F population) 0.05 for weeks 0-8 for TEZ/IVA+BSC (F/RF population), 0 afterwards
Annual rate of treatment discontinuation	EVOLVE/EXPAND used for trial period. Zero annual rate of treatment discontinuation assumed afterwards. The compliance to CFTR modulator therapies is assumed to be that observed in IVA patients in a real-world setting (80%) (39)	TEZ-IVA+BSC Discontinuation rate of 0.081 for F/RF population and 0.143 for F/F population during trial duration, 0 afterwards. Compliance =80%
Lung transplantation proportion	The model assumes that once a patient's ppFEV1 drops below 30%, the patient becomes eligible to receive a lung transplant. This was based on The UK clinical guideline for transplantation suggests referral for a lung transplantation for patients with ppFEV1 <30% (American Thoracic Society 1998 (40), Royal Brompton & Harefield 2011(41)). Whether an eligible patient will receive a lung transplant is influenced by a number of factors, including whether the patient meets the requirements for the waiting list, the availability of a matching donor organ, and the patient's health status; however, the model is not capable of estimating which patient receives a transplant at this level of detail. Thus, the percentage of eligible patients who receive a lung transplant was estimated to be 18.3% based on data from the 2015 UK CF Registry	18.3% of patients with ppFEV1<30%
Post lung transplantation mortality	The post-lung transplantation mortality is assumed to be 15.2% in the first year after the transplantation and 5.4% for each subsequent year. These estimates were derived from data collected from 7,815 adult patients with CF (all genotypes) who received a lung transplant between 1990 and 2014, with median survival of 8.9 years (The International Society for Heart and Lung Transplantation 2016 (42)).	15.2% in year 1 5.4% for each subsequent year

At baseline in the simulation, an individual patient's characteristics are compared to the characteristics of the reference population (i.e., the UKCFR) to compute a hazard ratio for that patient at baseline using the CPH model. The hazard ratio is then used to adjust the age-specific hazard from the reference population to derive the individual patient's mortality hazard at baseline. CPH model coefficients and mean reference values are presented in Table 16. Most of the reference values are based on the UKCFR with the exception of weight-for-age z-score derived from Liou et al 2001 (31) and calculated interaction of exacerbations and *B.cepacia*. Continuing the projection requires adjusting the hazard to reflect progression in any of the risk factor values (e.g., increasing of age by one model cycle, deterioration of lung function reflected in a lower ppFEV1) for that particular patient. This is achieved by calculating the hazard ratio with respect to that patient's own values at the beginning of the time interval that just

concluded. In other words, the reference values from the UKCFR are only used for the baseline hazard, whereas the patient's individual hazard at a previous cycle is used as a reference in the subsequent cycle.

Table 16 Cox Proportional Hazard model (CPH) predictors and mean reference values

Covariate	Coefficient (43)	SE (43)	Mean Reference Value (Reference)
Age (per year)	0.011	0.0049	19.6 (19)
ppFEV1 (per percentage point)	-0.042	0.0025	73.2 (44)
Sex (female = 1)	0.15	0.074	0.467 (44)
Weight-for-age z-score	-0.28	0.041	-0.850 (43)
Pancreatic sufficiency (yes = 1)	-0.14	0.23	0.126* (45)
Diabetes mellitus (yes = 1)	0.44	0.098	0.187 (46)
S. aureus (yes = 1)	-0.25	0.09	0.179 (19)
B. cepacia (yes = 1)	1.41	0.19	0.034 (19)
Annual number of acute exacerbations (max 5)	0.35	0.024	0.700 (19)
Exacerbations × *B. cepacia*	-0.28	0.06	Calculated†

Abbreviations: B. cepacia = Burkholderia cepacia, CPH = Cox proportional hazards, max = maximum, ppFEV1 = percent-predicted forced expiratory volume in one second, S.aureus = Staphylococcus aureus, SE = standard error, UK = United Kingdom *Estimated based on the % of patients not requiring a pancreatic supplement †Assumed equal to mean Burkholderia cepacia x mean acute exacerbations

Source: Liou et al(Liou 2001), UK CF Registry Annual Data Report 2008(Cystic Fibrosis Foundation 2009), UK CF Registry Annual Data Report 2012(Cystic Fibrosis Foundation 2013), US CF Registry Annual Data Report 2011(Cystic Fibrosis Foundation 2012).

The resulting overall survival curves are presented in Figure 13 - Figure 16. In the F/F population the median survival was 45.1 years in the TEZ/IVA arm and 38.4 years in the BSC arm. In the F/RF population, the median survival was 46.7 years in the TEZ/IVA arm and 39.8 years in the BSC arm.

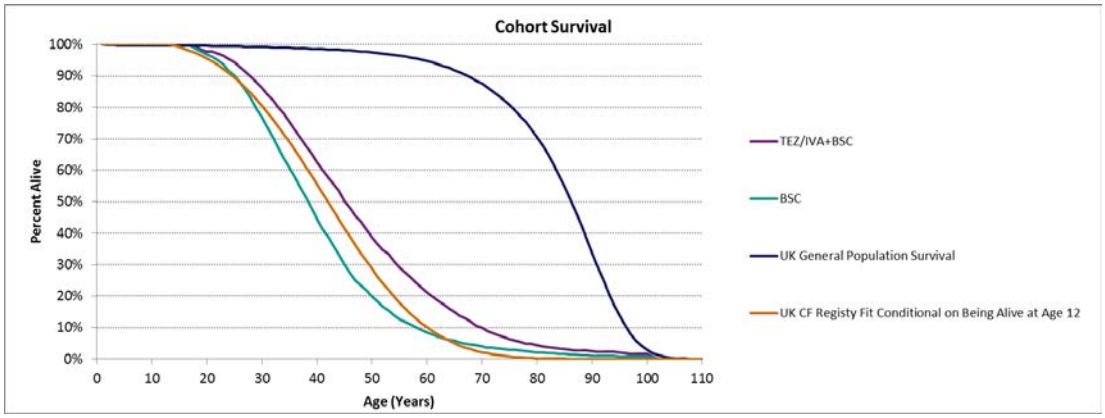


Figure 13 Survival output in the health economic model (F/F population). The reference curve is based on the UKCFR data extrapolated with the Weibull function. Survival is conditional on being alive at age 12

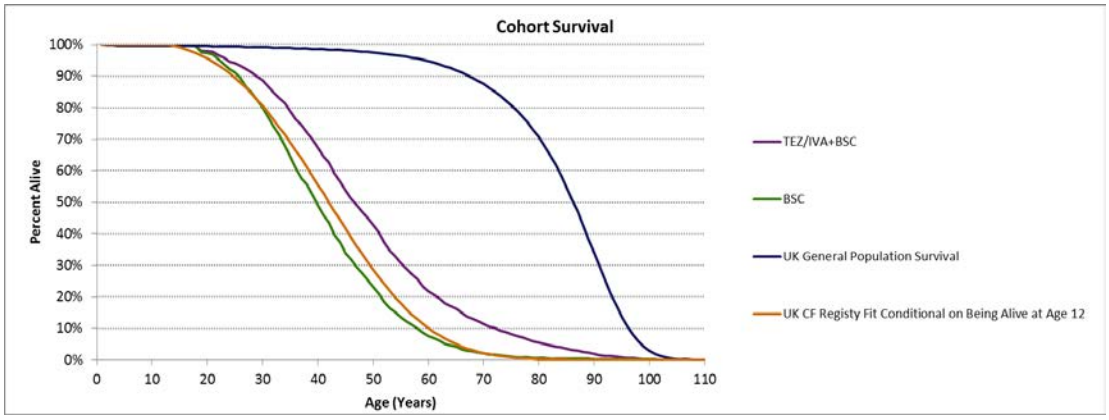


Figure 14 Survival output in the health economic model (F/RF population). The reference curve is based on the UKCFR data extrapolated with the Weibull function. Survival is conditional on being alive at age 12

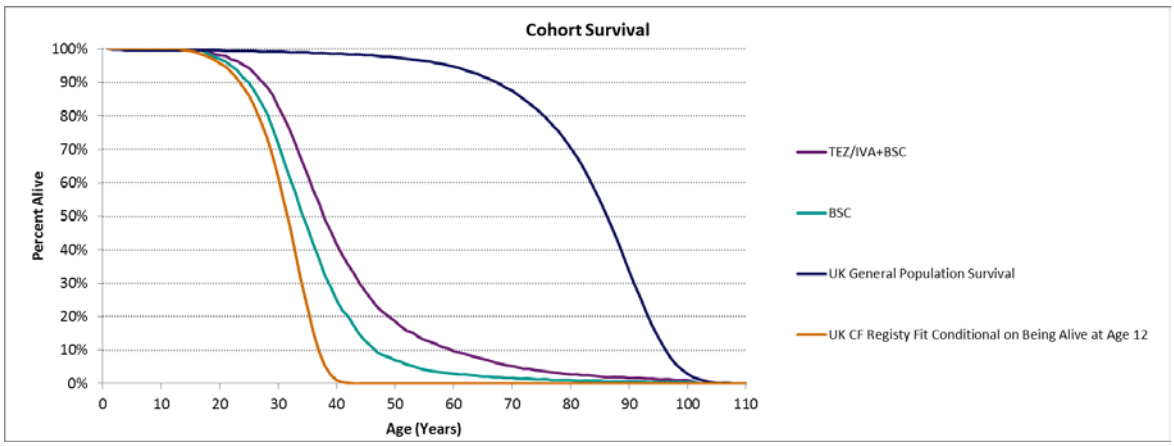


Figure 15 Survival output in the health economic model (F/F population). The reference curve is based on the UKCFR data extrapolated with the Gompertz function. Survival is conditional on being alive at age 12

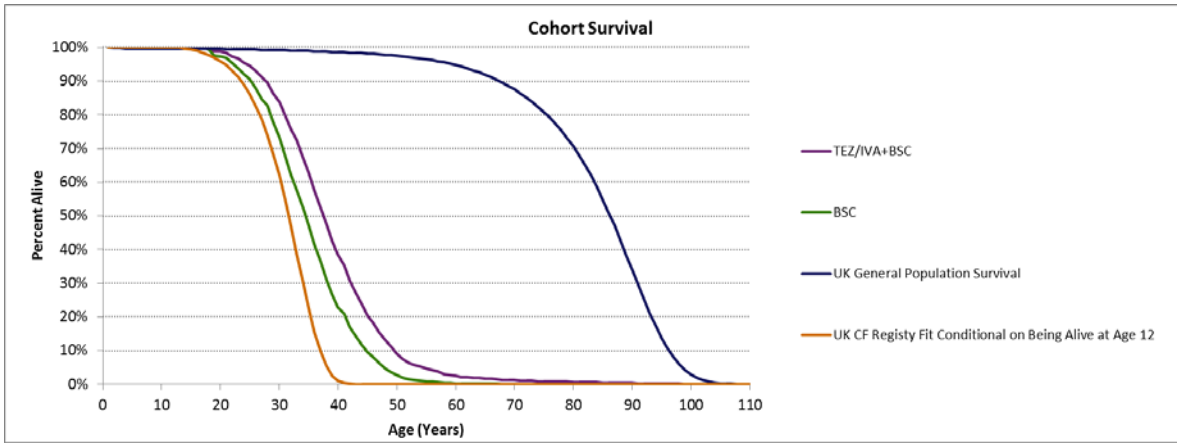


Figure 16 Survival output in the health economic model (F/RF population). The reference curve is based on the UKCFR data extrapolated with the Gompertz function. Survival is conditional on being alive at age 12

Updated base-case submitted by Vertex on 22nd of October 2019:

Vertex informed NoMA that they wanted to update their base-case with a new treatment effect of TEZ/IVA on ppFEV1 based on 96-week data from Study 110. Other parameters like PEx and discontinuation rate after week 24 and week 8 were not updated. Vertex submitted an analysis which they had performed to calculate ppFEV1 decline rate. In the first base-case, TEZ/IVA was assumed to decrease ppFEV1 decline rate by 42% in F/F patients and 47.1% in F/RF patients. In their updated base-case Vertex applied a decline rate reduction of 61.5% for both populations.

To evaluate the impact of TEZ/IVA on long-term "rate of change", a post-hoc analysis was conducted comparing the rate of ppFEV1 decline (slope) between F/F patients receiving TEZ/IVA in EVOLVE with propensity score-matched F/F mutated untreated control patients from the US registry (Cystic Fibrosis Foundation Patient Registry; CFFPR; years 2014-2016) (47). Vertex considered that the available sample size for the untreated controls with F/RF genotype in the CFFPR was too small and that it had insufficient power (less than 50%), hence an analysis in this population was not performed.

Vertex used the same methods applied to Study 110 as previously described in this report for the PROGRESS study (follow-up study in the LUM/IVA study program), using a combination of clinical trial and registry data (34, 35). Candidate variables for propensity score estimation were based on identified risk factors related to lung function decline at baseline (Table 17).

Table 17 Candidate Variables for Propensity Score Estimation

Demographics	Clinical Characteristics	CF-Related Medications
Age at baseline visit (years)	Height z-score	Tobramycin inhalation
Sex	Weight z-score	Colistin
Race	BMI z-score	Aztreonam
	BMI (actual)	Dornase Alfa
	Cystic Fibrosis-Related Diabetes	Acetylcysteine or Mucomist
	MRSA positive	Oral corticosteroid
	MSSA positive	Inhaled corticosteroid
	Haemophilus influenzae positive	Leukotriene modifiers
	Pseudomonas aeruginosa positive	Mast cell stabilizers
	Burkholderia positive	
	Alcaligenes positive	
	Stenotrophomonas positive	
	Aspergillus positive	
	Non-tuberculous mycobacterium positive	
	$ppFEV_1$	
	ppFVC	
	$ppFEF_{25-75}$	
	$ppFEV_1$/FVC ratio	
	$ppFEV_1$ decile	

To be eligible for this rate of change analysis, TEZ/IVA patients had to have 3 or more non-missing ppFEV1 measures recorded over a period of ≥ 6 months and at least 1 matched control from the US CFFPR (target of up to 1:5 matching). The inclusion criteria for the registry controls were as follows:

- Confirmed CF patients with valid sex, race and birth year available
- Diagnosed with CF with a F/F mutation at baseline
- At least 12 years of age
- No evidence of lung transplant or death from birth through the end of the baseline year
- No evidence of pregnancy in the baseline year
- ≥3 non-missing FEV1 records spanning ≥6 months through the last year of the three year period
- At least one "stable" encounter in the baseline year with valid nutritional (height-for-age, weight-for-age, and BMI z-score) and pulmonary function test

"Stable encounter" is required to mimic the clinical trial inclusion criterion of "stable CF disease." It was defined as an encounter (or visit) with no material change in lung function or routine medication from the prior encounter, and no evidence of a care episode. The visit utilised as baseline for each patient was randomly selected from stable encounters during the baseline year (2012).

Because the Global Lung Initiative (GLI) equations are used to calculate ppFEV1 in the CFFPR, and for consistency with previously published analyses (34, 35), GLI equations were also used to calculate ppFEV1 for this rate of change analysis. The calculated decline rate was 61.5% for F/F patients. Since a decline rate for F/RF patients could not be calculated according to Vertex, the rate of 61.5% calculated for F/F patients also was applied for this group.

NoMA´s assessment

Initial base-case submitted by Vertex on 21-Dec-2018:

Patients were only followed for 24 and 8 weeks in the EVOLVE and EXPAND studies. Taking into account that treatment of CF is lifelong, and that EMA (4) recommends a minimum of a 12 month FEV1 endpoint for therapies aiming to slow or stop pulmonary disease progression, NoMA considers the follow-up time in the pivotal trials too short to demonstrate a lasting effect compared to BSC. Evaluating the clinical importance of the ppFEV1 results from the TEZ/IVA studies is challenging, and Vertex themselves removed responder analysis for ppFEV1 from the EXPAND study protocol because it is difficult to interpret in the absence of an identified and validated minimal clinically important difference in the ppFEV1 (8).

The company presented a microsimulation model where characteristics of an individual patient were updated as they move throught the model. As mortality has not been captured in the trials, a survival equation depending on patient characteristics has been developed by Liou et al (31) and used in the model.

Parametric survival curves

Vertex has used a reference survival curve based on the UKCFR data to extrapolate relative survival in the model. Vertex states that multiple data cohorts were examined and standard parametric functions were tested to extrapolate long-time survival. Ultimately, the final analyses were based on the 1985–2008 birth cohort. The Weibull survival function was selected to be the best fitting parametric distribution, with a median predicted survival of 40.8 years. The model also offers the selection of the Gompertz function which gives a median predicted survival of 31 years. The choice of the survival cohort and the parametric function have certain limitations.

Survival in CF improved over the years (47) and it is not credible to use 1985-2008 birth cohort in the model. The predicted median survival for years 2013-2017 form the whole UKCFR is 47 years (48). In the recent US Cystic Fibrosis Foundation Report from 2017, the median predicted survival for years 2013-2017 was about 43 years (47). However, it is noted that the survival data from later birth cohorts is too immature to reliably reflect long-term survival.

It is noted that the reference curve is based on all CF patients irrespectively of the mutation status. This is accepted as the survival in patients with F/F mutation is expected to be lower or similar to other mutations (49, 50), and since we lack a better estimate for both the F/F and the F/RF population.

Although the company claims to have tested all standard parametric functions, only the selection of two was offered in the model. NoMA requested an overview of the mathematical and visual fit of the remaining standard parametric functions to the UKCFR data. Instead, Vertex submitted parametrisation of survival data from Cystic Fibrosis Registry of Ireland (2013). Extrapolation of the Irish CF survival curves with the best fitting Gompertz function produced median predicted survival of 39.9 years which is similar to 40.8 years as derived from the application of the Weibull function to the UKCFR data. The survival in the Norwegian practice has not yet been recorded for sufficient time to validate those extrapolations. However, according to the Norwegian clinical experts who were presented with the parametrisation of the KM curves from the 1985–2008 birth cohorts from UKCFR, a survival curve between the Weibull and the Gompertz function (Figure 12, right) would be more appropriate. The choice of the reference curve does not affect the results to a high degree in the F/F population (2.3% relative change in ICER for the selection of Weibull vs Gompertz) but does so in the F/RF population (3.7% relative change in ICER). When the reference curve is extrapolated with the Weibull function the resulting survival in the BSC curve is aligned to the reference or slightly worse. This is plausible. On the other hand, when the Gompertz function is chosen for extrapolation, the survival in the BSC is higher than in the reference curve which is not considered clinically plausible.

Consequently, NoMA accepts extrapolation of the 1985-2008 birth cohort with the Weibull function for the reference curve.

Patient characteristic variables
The Liou et al (31) equation (CPH model) was used to modify the reference curve survival by including individual patient characteristics. The equation was common for the F/F and the F/RF populations. The presence of zero, one, or two F508del alleles was tested for inclusion in the CPH model. However, this covariate was not found to be a significant predictor of mortality, indicating that the effect of the genotype on mortality is mediated through the phenotypic characteristics that were identified as significant predictors. Overall CFTR mutation classes I-III (including the F/F mutational status) are considered to cause more severe illness and insufficient pancreatic function than classes IV and V (including the F/RF mutational status), although clinical presentation is individual (12). It is likely that CFTR mutation status is a confounder (i.e affecting both the covariates and the outcome) but this has not been explored in the publication (Liou et al). Therefore, NoMA believes that adding genotype as an additional covariate in the equation may be relevant despite the lack of statistical significance.

The Norwegian experts contacted by NoMA confirmed that the predictors included in the Liou equation are clinically relevant. However, an important factor, the presence of PA (*P. aeruginosa)* infection, was omitted from the CPH model due to lack of statistical significance. PA is the most common airway pathogen in adult CF patients. PA colonization predicts lower FEV1, and a greater rate of decline in pulmonary function over time (51). Although the clinical relevance of PA is recognized, NoMA notes that 317 potential predictors were initially considered based on clinical rationale. The number of predictors

had to be limited given the sample size of 11,639 patients. The selection of variables in the final model based on statistical significance is therefore accepted.

Deterministic sensitivity analysis shows that the results of the health economic analyses are sensitive to age-dependent ppFEV1 rates of decline and the TEZ/IVA treatment effect after 24 weeks as well as to parameter *α* from PEx rate equation for patients ≥ 18 years (Table 15).

Decline in ppFEV1

Vertex has sourced the rate of annual ppFEV1 decline from a poster by Sawicki et al. (2017) (52). The research was based on a retrospective cohort of patients in the US CF Foundation Patient Registry (CFFPR) from 2006 to 2014. The strong point of the research was that the rate of decline was reported by the genotype relevant to this STA. The ppFEV1 values were lower in the F/F population than F/RF population excluding R117H which is plausible, and the slopes are steeper for the F/F population which is expected (Figure 17). The method of data analysis via a repeated measures model that accounts for correlated data within patients is also endorsed. The limitation of this approach is, however, that patients included in the analysis were between 6-45 years, and that only one rate of decline was applied to patients over 25 years old in the model. NoMA considers this an oversimplification as a proportion of 70 years old patients is still alive in the model.

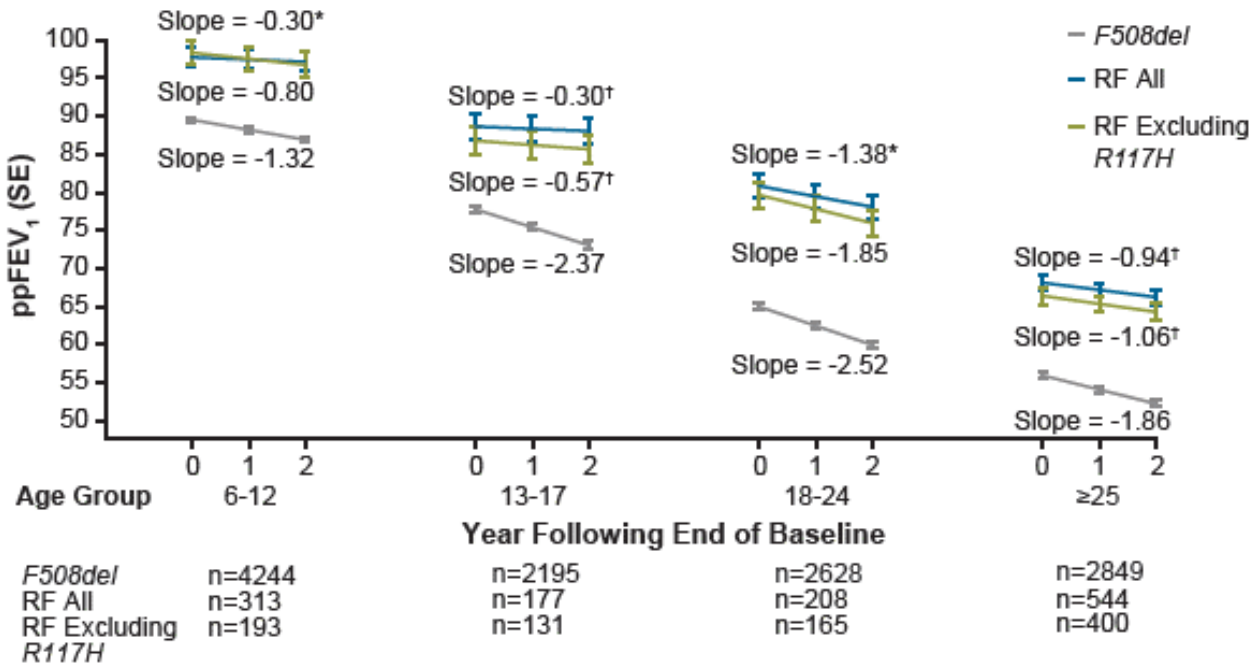


Figure 17 Intercept and slopes (rate of decline) of ppFEV1 by mutation and age group sourced from Sawicki et al (2017) (42).

NoMA has compared the modelled annual decline in ppFEV1 for the F/F and F/RF genotypes to data from international registries based on all mutations. In the model, the annual decline is the greatest between 13-24 years (F/F) or between 18-24 years (F/RF), after which the annual decline slightly decreases. Data from the Belgian registry based on 1,275 patients show that a stable decline in ppFEV1 is observed until year 30, next stabilizes and later increases again after year 50

Figure 18) (53). The trend in the UK registry based on 9,887 patients is similar although patients above 60 years old were grouped together preventing drawing conclusion on the long term trend (48). The ppFEV1 values from the registries are much higher than predicted in the model where the ppFEV1 at mean age 60 in the BSC arm is 15% in the F/F population and 25% in the F/RF population. As visualized in Figure 19 the rate of decline in the model is so high that the minimum threshold of 15% defined in the model is met at age 45 in the F/F population and at age 70 in the F/RF population (as visualized by flat line). Vertex argues that the output from the model cannot be compared to the registries. The model calculations were based on the rate of decline (the slope) as obtained from Sawicki et al (52). This study assessed within-subject change in ppFEV1 over time, allowing the estimate of the relationship between ppFEV1 and age (in terms of a slope). On the other hand, the plots from the registry reports are cross-sectional snapshots of ppFEV1 across age groups. The increase in ppFEV1 on a group level with older age does not necessarily mean that lung function improves in the UK registry, but rather that healthier patients who are still alive contribute to that increased value. It is difficult to properly estimate and interpret the age-ppFEV1 relationship using this kind of registry plot because subjects in each age group are different. NoMA agrees that model output based on longitudinal trends in ppFEV1 within the individual patient cannot be easily compared with the UK and Belgian registries that present a mean (or median, UK registry) value of ppFEV1 per age. Not being able to validate the results of the model is a considerable limitation of this STA. NoMA has tested the impact of a 20% smaller rate of decline on the ICER (see 4.2.3) and the impact is relatively small.

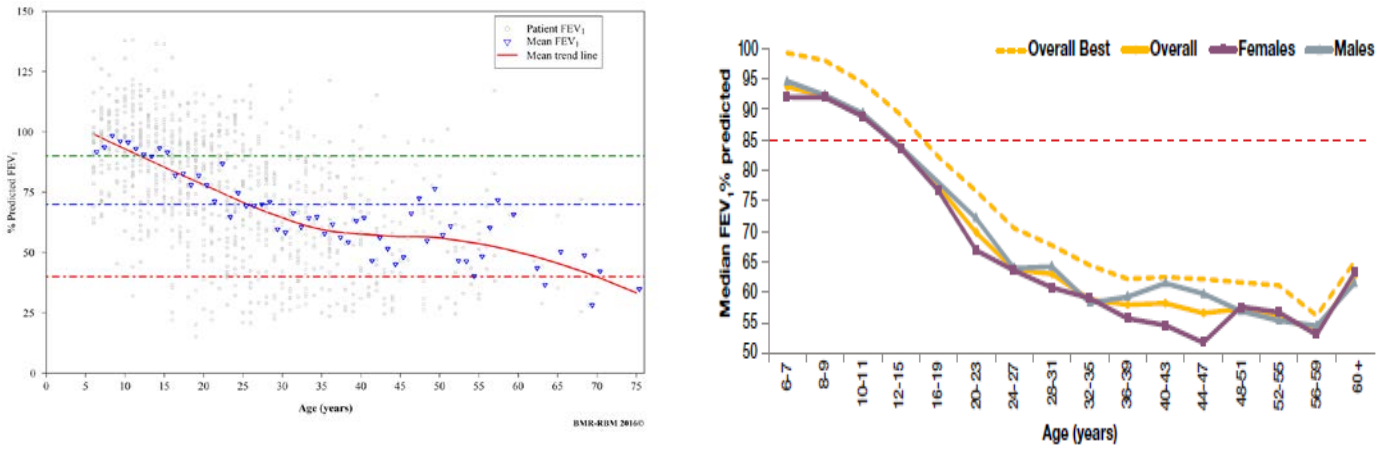


Figure 18 Mean ppFEV1 by age as sourced from the Belgian CF registry (left) (43) or the UK registry excluding patients with lung transplants, N=8168 (right) (38)

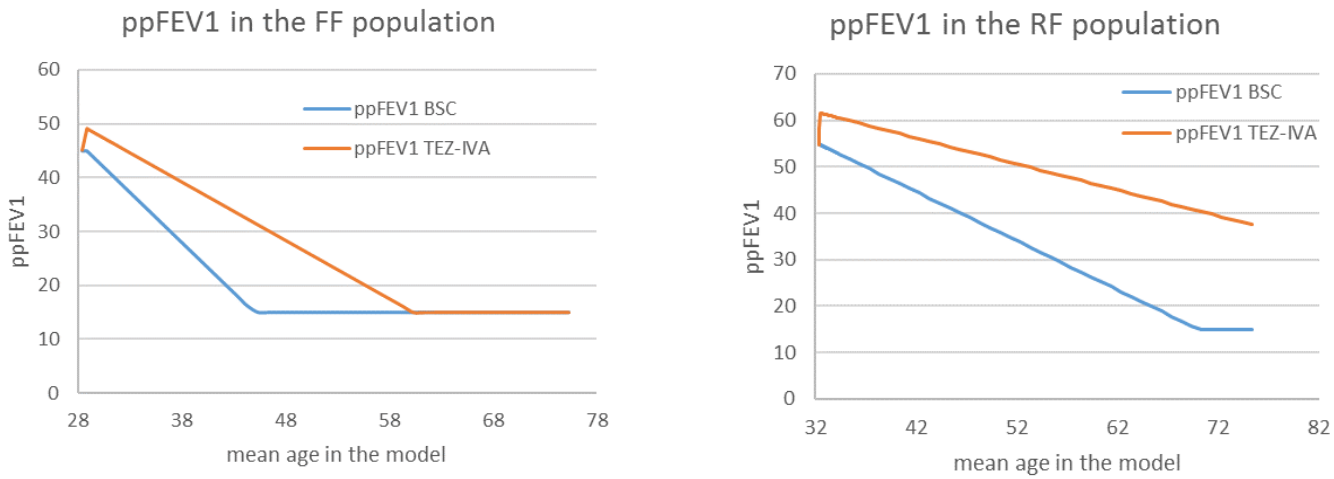


Figure 19 Mean ppFEV1 by mean age in the health economic model

Treatment effect of TEZ/IVA on ppFEV1

Treatment effects from the EVOLVE and EXPAND studies are used for the trial period in the models. After the trial period, treatment effects from external studies are used. For the F/F population model, it is assumed that TEZ/IVA reduces the rate of decline in ppFEV1 by 42% after week 24 in the model. This assumption was based on LUM/IVA effect on ppFEV1 as compared to a propensity score (PS)-matched cohort of patients from the US CFFPR in the F/F population (34). In the publication, the estimated annual rate of lung function decline was –1.33 percentage point (95% CI –1.80 to –0.85) in LUM/IVA -treated patients, significantly less than the rate in matched controls (–2.29 percentage points, –2.56 to –2.03, p<0.001). NoMA accepts the use of LUM/IVA data as a proxy for the effect of TEZ/IVA given the similarity of the products (Section 2.1.2). However, the reduction of 42% is only calculated for the 96-week follow-up period in the PROGRESS trial (part of the LUM/IVA study program) and the confidence intervals of the annual rate of decline are broad highlighting the uncertainty of the estimate. NoMA considers the two-year data to be too immature to reliably estimate the long-term effect of TEZ/IVA given the change in the long-term annual rate of ppFEV1 decline as observed in the Belgian and UK registries. Decreasing the treatment effect by 20% in the original model (using the treatment effect relative to BSC option) increased the ICER by around 300 000 NOK..

A respective reduction of 47.1% after week 8 was used in the F/RF model based on a similar PS-matched comparison in patients with *G551D* mutation treated with IVA (35). Interestingly the controlled cohort included only patients with homozygous *F508del* mutations. This could be potentially problematic as the treatment effect of IVA could be affected by the mutation status. However, a publication by Sawicki et al (2017) (54) indicates that slopes of lung function decline are similar between the genotypes. It is noted that TEZ/IVA was significantly better than IVA monotherapy in the EXPAND study. However, NoMA considers a reduction of 47.1% to be very uncertain as it is based on IVA in a different indication with a

follow-up of up to 3 years as compared to 8 weeks in EXPAND. The 95% confidence intervals for the difference of 0.80 in slopes between IVA and BSC are considered broad by NoMA (i.e 0.06, 1.55) highlighting the uncertainty of the results. Decreasing the treatment effect by 20% in the original model (using the treatment effect relative to BSC option) increased the ICER by around 90 000 NOK).

Modeling Pulmonary Exacerbations (PEx)

The PEx annual rate used in the model has not been directly sourced from the EXPAND or EVOLVE studies. Instead, it has been obtained via an age-dependent exponential regression equation with ppFEV1 as a variable. In other words, the pulmonary exacerbation rate is dependent on the ppFEV1 values used in the model. As ppFEV1 is modelled to be different between TEZ/IVA and BSC, the calculated PEx rate should reflect this difference. Nevertheless, Vertex applied an additional rate ratio of 0.61 of PEx relative to BSC in the F/RF model, and 0.53 in the F/F model based on rate ratios from the trials. To adjust for the potential of double-counting treatment effects for ppFEV1 and pulmonary exacerbation, calibration techniques were used to derive a pulmonary exacerbation rate ratio for TEZ/IVA relative to BSC that account for the impact of the acute improvement in ppFEV1. It is noted that the obtained rate ratios are based on short trials, and that PEx only was an exploratory endpoint in the EXPAND study. In EXPAND the number of events recorded within 8 weeks was low (20/161 for BSC vs 11/161 for TEZ/IVA) resulting in a very uncertain estimate of 0.54 with broad 95%CI of 0.26 to 1.13. NoMA has plotted the rates of exacerbation as predicted in the model (
Figure 20). As the rates are dependent on ppFEV1, a ceiling effect is visualized on the plot once ppFEV1 decline becomes stable.

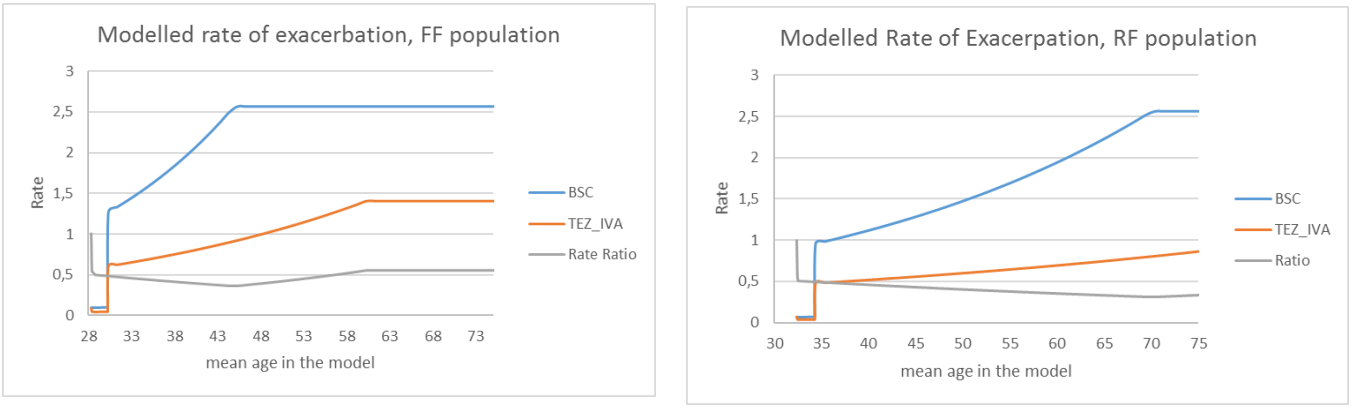


Figure 20 Modelled rate of exacerbation requiring IV antibiotics and/or hospitalization in the health economic model

NoMA has reviewed the key efficacy parameters and accepts the assumptions used by Vertex. However, it is noted that the EVOLVE study, and especially the EXPAND study, have very short follow-up time compared to the model horizon. The input values for the model are often based on highly uncertain estimates (broad CIs) sourced from external trials from other CTFR modulators. ppFEV1 is the key parameter in the model as it affects survival, the pulmonary exacerbation equation and the utility

equation (Section 3.3.3). Nevertheless, the model outputs in terms of ppFEV1 (and subsequently PEx) are very difficult to validate against available registries. A decrease of 20% in the rate of ppFEV1 decline for BSC or TEZ/IVA effect reduction has a small relative, but substantial absolute, impact on the ICER.

Updated base-case submitted by Vertex on 22nd of October 2019:

Treatment effect of TEZ/IVA on ppFEV1

Vertex has updated the estimate of treatment effect of TEZ/IVA on ppFEV1 in the F/F model based on the results from the final data cut off from Study 110.
Study 110 included 459 F/F patients from EVOLVE. The primary analysis included 443 patients as 16 patients left Study 110 to participate in another CFTR modulator study.
Vertex has conducted an indirect treatment comparison of the rate of ppFEV1 decline (slope) between F/F patients receiving TEZ/IVA with propensity score-matched CFTR mutated untreated control patients from the US registry. A total of 407 TEZ/IVA-treated F/F patients were matched with 1,383 registry control patients (on average 3.4 controls per TEZ/IVA-treated patient). A small fraction from the TEZ/IVA cohort (36/443 patients) was not matched. The groups were well balanced at baseline after propensity score matching (Table 18).

Table 18 Baseline Demographics, Clinical Characteristics at Baseline, and Study Duration for Matched TEZ/IVA and Control

Characteristic	TEZ/IVA (N=407)	Control* (N_w=407; N=1,383)
Age (in years), Mean ± SD	26.03 ± 10.35	26.04 ± 5.57
Age ≥18, n (%)	310 (76.2%)	310 (76.2%)
Female, n (%)	191 (46.9%)	182 (44.7%)
White/Caucasian, n (%)	402 (98.8%)	404 (99.2%)
CF-related diabetes (prior to baseline), n (%)	72 (17.7%)	75 (18.4%)
BMI, Mean ± SD	21.03 ± 2.97	21.13 ± 1.66
FEV_1 percent predicted (GLI) at baseline, Mean ± SD	58.95 ± 14.54	59.43 ± 9.25
<40, n (%)	45 (11.1%)	45 (11.1%)
40-70, n (%)	252 (61.9%)	252 (61.9%)
>70, n (%)	110 (27.0%)	110 (27.0%)
Pseudomonas positive, n (%)	292 (71.7%)	286 (70.4%)
Dornase alfa, n (%)	293 (72.0%)	307 (75.4%)
Inhaled corticosteroid, n (%)	152 (37.3%)	131 (32.1%)

*Weighted using the inverse of the number of controls in each match set, the calculation of the summary statistics in the control group accounts for this weighting.[5]

The estimated annualized rate of decline in ppFEV1 in TEZ/IVA and control groups were -0.80 (95% CI: -1.31, -0.30) and -2.08 (95% CI: -2.34, -1.82) percentage points, respectively (

Figure 1). This represents a mean difference of 1.27 percentage points (p<0.001) and a 61.5% reduction in the annualized rate of ppFEV1 decline in TEZ/IVA-treated F/F patients compared with matched F/F mutated untreated controls. NoMA welcomes the use of TEZ/IVA data in estimating the treatment effect. However, as commented previously on data from the PROGRESS study, NoMA considers the two-year data to be too immature to reliably estimate the long-term effect of TEZ/IVA.

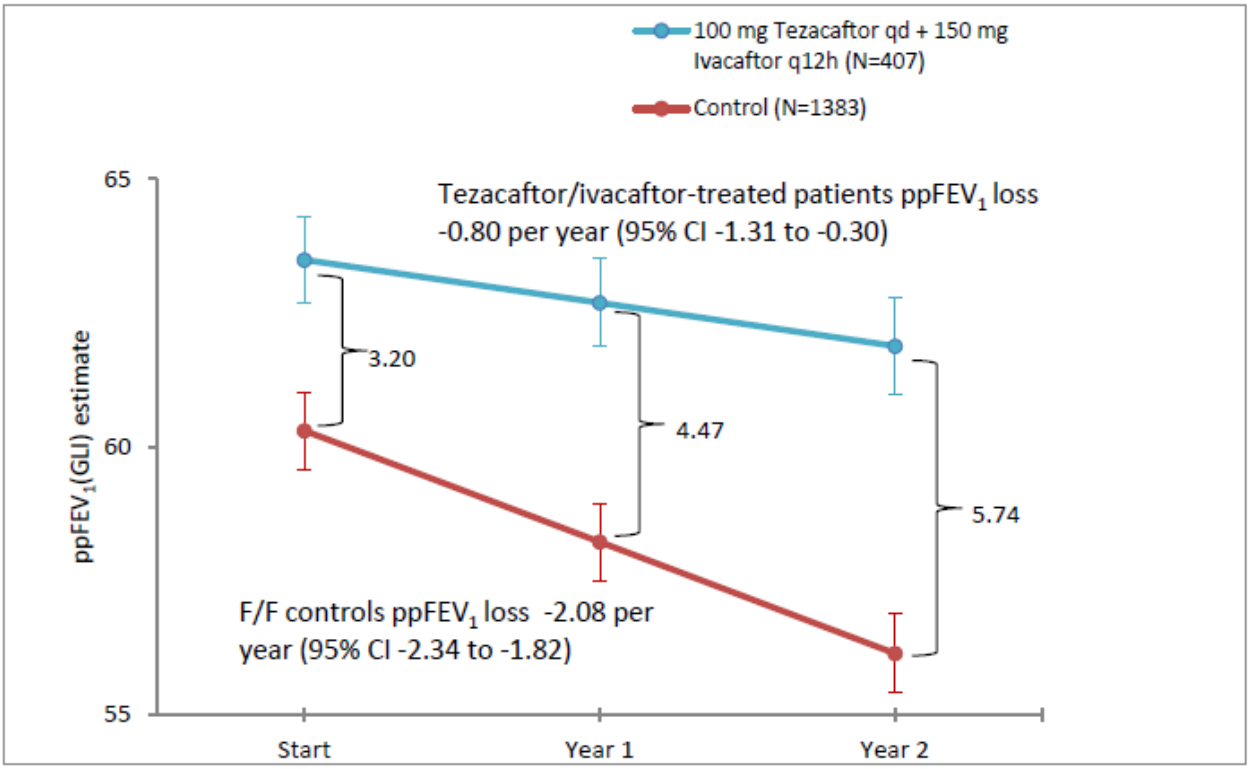


Figure 21 Estimated Annual Rate of ppFEV1 Decline with TEZ/IVA Compared with a Propensity-Matched Control Group

Vertex assumes the rate of decline for ppFEV1 to be equal between the F/F and F/RF populations, but has not presented any data supporting this assumption.

NoMA has checked model results for F/F and F/RF populations after two years (updated base-case with 61,5% treatment effect) for TEZ/IVA as compared to updated 110 trial results at approximately two years.

In the F/F population, the modelled increase in ppFEV1 after two years is 2.9 as opposed to about 2 based on Study 110 results. The application of a treatment effect of 61.5% in the model results in a rate of ppFEV1 decline of -0.72 for TEZ/IVA, which is smaller than the projected rate of -0.80 (95%CI -1.31-, -0.30) from the updated Study 110 (based on the patient population included in the propensity score analysis). Therefore, the effect of TEZ/IVA in the model seems to be overestimated for the F/F population with the new treatment effect of 61.5%. In the first base-case, which was based on a treatment effect of 42%, the modelled increase in ppFEV was 2.35 which is much closer to the empirical 2. However, the modelled rate

of decline in ppFEV1 in the first base-case of -1.08 for TEZ/IVA was much more conservative than the empirical rate of decline of -0.80. It must be noted, however, that these numbers cannot be directly compared as one is based on modelled ppFEV1 and the other on least square mean from Study 110.

It is a limitation that the modelled results cannot be easily validated. In conclusion, none of the treatment effects (updated 61.5% or former 42%) applied in the model results in ppFEV1 for TEZ/IVA that is fully aligned with the updated Study 110 results for the F/F population.

In the F/RF population, the modelled increase in ppFEV1 is 5,77 (former 47% treatment effect) or 6,05 (updated 61.5% treatment effect) for TEZ/IVA after two years as opposed to 7.05 in updated Study 110.

When updating ppFEV1 estimates in the model, PEx (dependent on ppFEV1 in the model) also changes. Modelled PEx cannot be validated.

NoMA accepts the use of the updated treatment effect of 61.5% in the F/F and the F/RF model. *The issues around external validation of the model outputs and uncertainty about long-term relative effect remain.*

Discontinuation rate:

In the models, 14.3% (F/F population) and 8.1% (F/RF population) of the patients, respectively, discontinue TEZ/IVA treatment after 24 and 8 weeks (i.e. duration of the EVOLVE and EXPAND studies). After 24 and 8 weeks, it is assumed in both models that all patients will continue treatment with TEZ/IVA for as long as they live.

During the 96 week follow-up in Study 110, 107 (13.5%) of the 789 included patients with F/F and F/RF genotype discontinued TEZ/IVA; 24 patients (3.0%) due to AEs and 83 patients (10.5%) due to reasons not related to AEs. The majority of these patients (685/789) were included from EVOLVE and EXPAND, and the rest of these patients were included from other TEZ/IVA studies for F/F patients. NoMA finds the discontinuation rates from Study 110 relevant and transferable for the modelled F/F and F/RF populations.

While the EVOLVE and EXPAND studies did not provide information about the impact of treatment withdrawal on ppFEV1, two other studies in the TEZ/IVA study programe did (studies 101 and 103). Changes in ppFEV1 after discontinuation of treatment showed that the improvements in ppFEV1 during 4 weeks of TEZ/IVA treatment were lost 1 to 4 weeks after discontinuation of dosing. However, as preservation of lung function by a CFTR modulator will need much longer time than 1 month, this loss of effect is not considered indicative for long-term effects (8).

It is uncertain whether the yearly discontinuation rate will alter after treatment year two, or if it will remain unchanged. Long-time users (i.e. patients who have used the drug for more than two years) may differ from patients who discontinue therapy earlier. NoMA does not believe that it is plausible that no patients discontinue TEZ/IVA after year two, but lacks an estimate for a yearly rate for long-time users. In addition, the model assumes that patients who discontinue TEZ/IVA immediately loose effect relative to

placebo (withdrawal effect as showed after short-term treatment as described above). Based on this, NoMA uses a discontiuation rate of 0% for the time period after Study 110.

Adding a discontinuation rate corresponding to data from Study 110 affects the ICER by removing costs and modelled benefit/effect for the period where patients no longer use TEZ/IVA. As a consequence the ICER increases with discontinuation.

NoMA's changes to the base-case based on new data submitted 22nd of October 2019.

NoMA accepts the use of the updated treatment effect of 61.5% in the F/F and the F/RF models, and applies a discontinuation rate of 13.5% over 96 weeks corresponding to Study 110 in addition to the discontinuation rates of EXPAND and EVOLVE.

3.3.2 Safety

Submitted clinical studies

EMA assessed safety for TEZ/IVA when granting MAA (8). Main safety data was derived from 496 patients who received TEZ/IVA and 505 patients who received placebo in TEZ/IVA phase 3 studies. Mean treatment duration was 16 weeks in both groups. Long-term safety of TEZ/IVA in patients with CF was presented from open label extension Study 110.

The rate of AEs leading to treatment discontinuation (1.6% TEZ/IVA vs. 2% placebo) or treatment interruption (2.4% vs. 3.6%) was low and balanced. Infective PEx of CF was the most common AE leading to treatment discontinuation, which could be expected for patients with CF.

EMA concluded that no significant new or additional safety concerns were identified with the addition of TEZ to IVA. The safety profile of TEZ/IVA appeared similar across studies. There were no latent, late-onset safety issues or risks identified in the long term safety sets.

Table 19 AEs with an incidence of at least 5% in either treatment group by preferred term

Preferred Term	Placebo N = 505 n (%)	TEZ/IVA N = 496 n (%)
Subjects with any AEs	439 (86.9)	408 (82.3)
Infective pulmonary exacerbation of cystic fibrosis	153 (30.3)	117 (23.6)
Cough	141 (27.9)	108 (21.8)
Headache	57 (11.3)	68 (13.7)
Nasopharyngitis	49 (9.7)	57 (11.5)
Sputum increased	65 (12.9)	57 (11.5)
Haemoptysis	56 (11.1)	48 (9.7)
Pyrexia	49 (9.7)	41 (8.3)
Fatigue	51 (10.1)	38 (7.7)
Nausea	34 (6.7)	38 (7.7)
Oropharyngeal pain	44 (8.7)	36 (7.3)
Diarrhoea	34 (6.7)	31 (6.3)
Dyspnoea	36 (7.1)	30 (6.0)
Abdominal pain	34 (6.7)	29 (5.8)
Nasal congestion	28 (5.5)	24 (4.8)

Source: ISS/Table 2.1.2.2.3

AE: adverse event; IVA: ivacaftor; PC-SS: Placebo-controlled Safety Set; PT: preferred term; TEZ: tezacaftor

Notes: A subject with multiple events within a category is counted only once in that category. Table is sorted in descending order of TEZ/IVA column by PT. The PC-SS includes all subjects who received at least 1 dose of TEZ/IVA or placebo in Studies 106, 107, or 108. Subjects from Study 108 may receive 2 periods of treatment due to the cross-over design and therefore may be counted in more than 1 column. MedDRA Version 19.1.

Vertex submitted updated safety data 22nd of October derived from 1042 patients included in the 110 study, from the final cut off at 96 weeks. The table below shows an overview of treatment emergent adverse events (TEAEs). No new safety concerns were identified.

Table 20 Overview of TEAEs from Study 110 after 96 week follow up (Source Vertex)

Patients, n (%)	Safety Set N=1042
Any TEAEs	995 (95.5)
TEAEs by strongest relationship	
Not related	439 (42.1)
Unlikely related	286 (27.4)
Possibly related	245 (23.5)
Related	25 (2.4)
TEAEs by maximum severity	
Mild	249 (23.9)
Moderate	552 (53.0)
Severe	191 (18.3)
Life threatening	3 (0.3)
TEAEs leading to treatment discontinuation	22 (2.1)
Serious TEAEs	351 (33.7)
TEAEs leading to death	0

Submitted health economic analyses

The health economic model includes all AEs that occurred in at least 5% of the TEZ/IVA arm of the EXPAND or EVOLVE study, and where the incidence in the CFTR-modulating arm was at least 1 % higher than in the placebo arm (expressed as number of AEs per person-year).

For the F/F-population, the annual AE incidence rates are calculated based on the EVOLVE study. For the F/RF population, the annual AE incidence rates are calculated based on the EXPAND study.

Table 21 Modelled annual AE incidence rates

Adverse event	F/F-population		F/RF-population	
	TEZ-IVA + BSC	BSC	TEZ-IVA + BSC	BSC
Diarrhoea	-	-	0.544	0.414
Nausea	0.208	0.157	-	-
Nasopharyngitis	0.397	0.355	0.544	0.204
Headache	0.418	0.355	0.811	0.544
Sputum increase	-	-	0.587	0.457

Abbreviations: BSC: best supportive care, F508-del: TEZ-IVA: tezacaftor-ivacaftor (Symkevi)

AE costs are considered in the health economic model, see section 4.1.3.

NoMA´s assessment

According to the EMA guideline on the clinical development of medicinal products for the treatment of CF (4), safety is difficult to assess in CF patients, because of the debilitating underlying disease and a large number of concomitant medications.

In the health economic model, different rates of AEs are assumed for F/F and F/RF populations, based on data from the EVOLVE and EXPAND studies. Data from the follow-up safety study is not used in the model. When informing the models with study specific AE data, Vertex assumes different AE rates for patients with different genotypes. However, EMA concluded there were no meaningful differences in in the safety profile of TEZ/IVA in EVOLVE and EXPAND (8).

AEs were modelled based on pre-defined inclusion criteria, e.g. all AEs that occurred in at least 5% of the TEZ/IVA patients with an incidence of at least 1% higher than the placebo arm are included. With this approach the company has included 3 AEs for the F/F population and 4 AEs for the F/RF population. All other AEs were excluded from the model.

If AEs had been modelled based on the main safety set and Vertex' criteria, only headache (13.7% vs 11.3%) and nasopharyngitis (11.5% vs 9.7%) would have been included in the model. In the model costs are applied to AEs (per event). As the modelled events are relatively cheap to treat, altering the incidence rates does not affect the ICER with any significance.

TEAEs leading to discontinuation of TEZ/IVA are described and assessed in chapter 3.3.1.

Based on the low impact costs for AEs have in the model, NoMA has not made any changes to the way AEs are modelled.

3.3.3 Health Related Quality of Life (HRQoL)

Submitted documentation

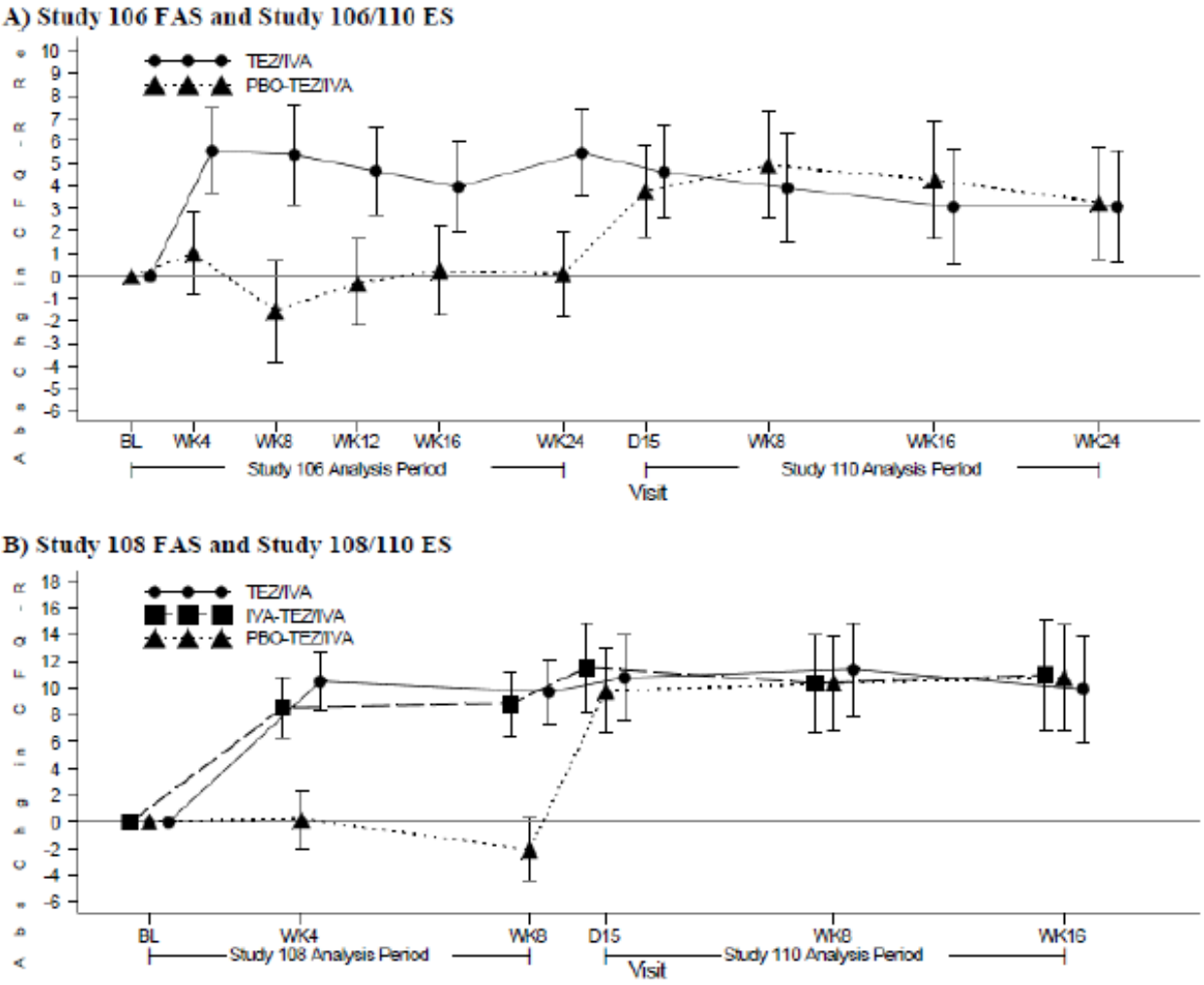
Cystic Fibrosis Questionnaire-Revised (CFQ-R) is used to measure overall health, daily life, perceived well-being, and symptoms in CF patients. Several questions included in the CFQ-R assess overall HRQoL. A higher score indicates better HRQoL.
Figure 22 shows CFQ-R results for EVOLVE (study 106), EXPAND (study 108) and Study 110.

Vertex has split the CFQ-R score in dimensions regarding respiratory and non-respiratory domains. The non-respiratory consist of dimensions such as physical-, role- and emotional-functioning, vitality, eating disturbances, weight, and digestive symptoms. The respiratory domain refer to the CFQ-R questions regarding respiratory symptoms.

In week 8 of the EVOLVE study, 53.9% of the TEZ/IVA patients had an improvement of 4 points in the CFQ-R respiratory domain score. This change has been considered as clinically relevant. After 16 weeks of treatment with TEZ/IVA, the proportion of patients with a clinically relevant change was 62.2%. In week

24 of the EVOLVE study, 51.3% of the TEZ/IVA patients and 35.7% of the patients in the placebo arm had an improvement of 4 points in the CFQ-R respiratory domain score. After 48 weeks of treatment with TEZ/IVA, the proportion of patients with a clinically relevant change was 48.6%.

In the EXPAND study, the TEZ/IVA patients had a 11.1 points improvement in the respiratory domain score of CFQ-R after having received TEZ/IVA for 8 weeks. Patients that participated in the placebo arm in the EXPAND study and were treated with TEZ/IVA in the follow-up Study 110 improved by 11.2 points on respiratory domain score after 96 weeks with TEZ/IVA. Figure 24 indicates that these improvements lasted throughout the study period of Study 110.



Sources: ISE Figure 3.4.1.1 (Study 106); ISE Figure 3.4.1.2 (Study 108)
BL: baseline; CI: confidence interval; D: day; ES: Efficacy Set; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; PBO: placebo; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor; Wk: week
Study 106: During Study 106, the last non-missing measurement before the first dose of study drug in Study 106 was used to calculate the change from baseline. For subjects in the PBO-TEZ/IVA group, the last non-missing measurement before the first dose of study drug in Study 110 was used to calculate the change from baseline during study 110.
Study 108: For both the Study 108 and 110 Analysis Periods, baseline was the most recent non-missing measurement before the first dose of study drug in Study 108. Treatment assignment in this period was based on assigned treatment in Period 2 of Study 108. Study 108 Analysis Period includes Treatment Periods 1 and 2, and subjects were included in more than 1 treatment group during the Study 108 Analysis Period.

Figure 22 Absolute change in CFQ-R Respiratory Domain score in EVOLVE + studie 110 (A) and EXPAND + Study 110 (B) (5)

Follow-up data at 96 weeks indicate a change of 3 (0.7-5.3) compared to EVOLVE baseline on the respiratory domain score for 208 patients of the F/F population (Figure 23). Patients with an F/RF group

mutation (n= 67) had an absolute change of 13.8 (10.3-17.2) at 96 weeks compared to the EXPAND baseline (Figure 24).

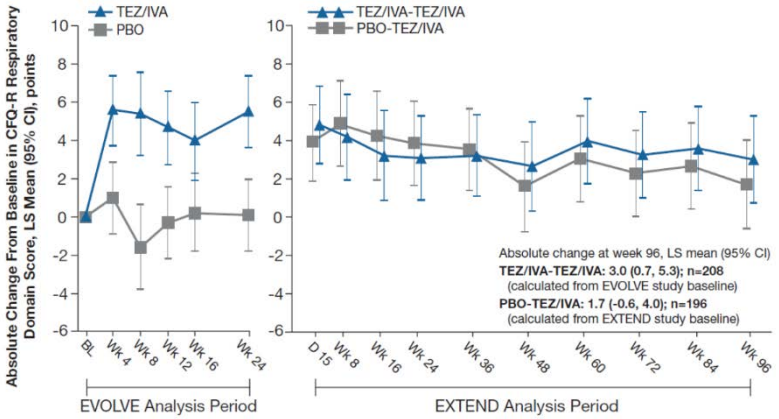


Figure 23 Absolute Change from EVOLVE Baseline in CFQ-R Respiratory Domain Score in the 106/110 Efficacy Set (F/F)

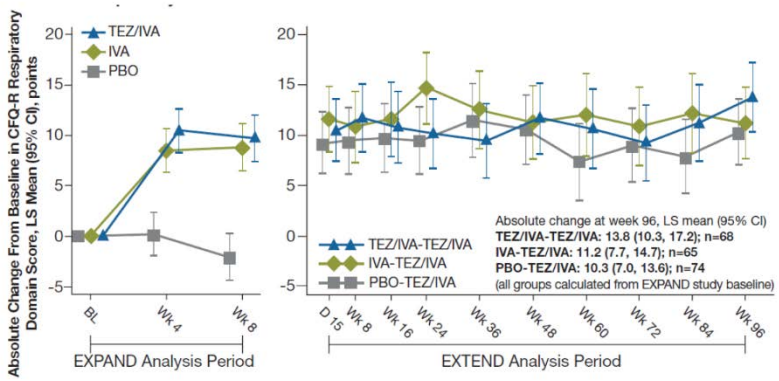


Figure 24 Absolute Change from EXPAND Baseline in CFQ-R Respiratory Domain in the 108/110 Efficacy Set (F/RF)

SF-12

The 12- Item Short Form Survey (SF-12) results are used to estimate a preference-based measure of health utility.

In order to measure health utilities, the SF-12 data collected in the EXPAND, EVOLVE study and in Study 110 have been transformed into SF-6D utilities using an approach provided by Brazier and colleagues In EVOLVE, SF-12 was assessed at day 1, week 4, week 8, week 12, week 16, and week 24. In EXPAND, SF-12

was assessed at day 1, week 4 and week 8 for treatment period 1, and week 16, week 20, and week 24 for treatment period 2. At baseline patients had a utility of 0.81 which was estimated based on the SF-6D utilities collected in the EVOLVE and EXPAND study. SF-6D utilities were age-adjusted using the multiplicative UK SF-6D tariff per age group.

EQ-5D has not been applied and SF-6D utilities have not been mapped onto EQ-5D utilities.

Submitted health economic analyses

SF-6D utilities are not used as direct inputs in the health economic model. Instead, a utility equation was used to predict how SF-6D utilities vary with the $ppFEV_1$ and the occurrence of pulmonary exacerbation and the cumulative number of exacerbations. Vertex used a multivariable mixed-model repeated measures regression analysis to model the relationship between SF-6D utilities, $ppFEV_1$ and pulmonary exacerbation which were collected from 504 samples in EVOLVE over a 24-week period.
Vertex assumes that this utility equation only captures changes in health utilities which are related to respiratory outcomes ($ppFEV_1$, pulmonary exacerbations). In order to capture the impact of non-respiratory outcomes, an additional utility increment of 0.043 has been added to patients who received TEZ/IVA. The size of the utility increment was derived from mapping the CFQ-R non-respiratory domains to EQ-5D utilities as described in Acaster and colleagues (55).

Utility continuous equation

β_0 (Intercept)			0,575
β_1 (First-Order of $ppFEV_1$)			0,675
β_2 (Second-Order of $ppFEV_1$)			-0,434
β_3 (First-Order of Cumulative Number of Exacerbations)			-0,012
β5 (Dummy Explanatory Variable)			0,043

The model also gives opportunity to use utilities by ppFEV1 strata. The utilities are summarised in the table below.

Utilities by health state (ppFEV strata) from EVOLVE/EXPAND.

$ppFEV_1$ Strata	Utility Value
≥90%	0,835
70 %-89%	0,835
40%-69%	0,808
<40%	0,773

Post-lung transplant utilities used in the model are based on EQ-5D utilities from previous studies (56-58). The post-transplant EQ-5D utility used in the model is 0.81.

NoMA´s assessment

NoMA acknowledges that measuring health utilities with a generic preference-based instrument is challenging in the CF population. Patients with CF report higher health utilities than would be expected based on disease severity (59). EQ-5D has shown ceiling effects when used in the TRAFFIC and TRANSPORT studies. With EQ-5D utilities ranging from 0.91 to 0.94 at baseline it is important to evaluate which aspects of disease burden have not been captured with EQ-5D or other generic preference-based HRQoL instruments. One possible explanation for these ceiling effects is an adapted frame of reference in the CF population, which means that their reference point of "full health" can differ from general population. This adaption effect makes it difficult to compare utilities reported by CF patients with health utilities reported by the general population or other patient groups.

In addition to these general challenges related to measuring HRQoL in CF patients, NoMA has discovered several shortcomings in Vertex's assessment of HRQoL:

- *Choice of instrument:* Use of SF-12/SF-6D instead of EQ-5D without justification for why SF-12/SF-6D resolves shortcomings of generic preference-based instruments' insensitivity in measuring HRQoL in CF patients.
- *Utility estimation approach*: Use of a utility equation to estimate health utilities in the model without presenting how the assumptions of using this approach have been tested and without providing empirical proof that the chosen equation fits the data.
- *Utility increment:* Adding a utility increment of 0.043 to TEZ/IVA arm to capture utility gain from non-respiratory domains of CFQ-R.
- *Coverage*: Relevant factors have not been captured in the utility equation. Using only ppFEV1 and the number of PEx as predictors of health utility, without capturing the adverse events and disutilites due to amount of time used for treatment.
- *Uncertainty*: It remains unknown if the data used to estimate health utilities for post-lung transplantation are informative for CF patients.

While being aware of these shortcomings, NoMA accepts the health state utilities used in the model, due to limited other sources of HRQoL data, except for the utility increment. The mentioned shortcomings are discussed below an explanation is provided why NoMA does not include the utility increment for patients in the TEZ/IVA arm in its own base-case. The issues discussed below are further explored in sensitivity analyses and NoMA's base-case (see chapters 4.2.1 & 4.2.3).

Choice of HRQoL instrument

Vertex argues that EQ-5D has shown ceiling effects and could not differentiate between patients in different ppFEV1 categories in earlier CF studies. Therefore SF-12 has been applied. No rationale has been given for why Vertex expects SF-12 to be more sensitive and showing less ceiling effects in CF patients. Even if SF-6D utilities are lower than the previously observed EQ-5D utilities, they are still considerably higher than what can be expected given the CF disease burden.

Vertex mentions an article by Acasterand colleagues (55) that provides EQ-5D utilities and CFQ-R scores for the UK CF population. Acaster estimated a mapping algortihm that allows to map between these two instruments (55). The average EQ-5D utility for total CF sample assessed in Acaster's study is 0.67 (±0.28). Despite the considerable standard deviation, there are clearly less pronounced ceiling effects in this study. In contrast to Vertex's argument about EQ-5D couldn't differentiate between FEV1 categories, the authors of this study find a clear correlation between patients utility in different FEV1 categories. :

> "Both the EQ-5D and CFQ-R mean scores reflect the self-reported disease severity as measured by FEV1, with utility and almost all CFQ-R domain scores declining with increased severity."

Vertex has not provided EQ-5D utilities mapped from CFQ-R values from EVOLVE/EXPAND. Neither have SF-6D utilities been mapped to EQ-5D as recommended in NoMA's guidelines. It would have been an option for Vertex to use the EQ-5D utilities published in Acaster to estimate health state utilities in the model when using the *ppFEV1 strata approach*. EQ-5D with UK tarriffs are recommended in NoMA guidelines and the FEV1 severity strata reflects the health states in the model. NoMA has explored the impact of using the EQ-5D utilities reported by Acaster and colleagues in a scenario analysis (see 4.2.3).

Table 22 EQ5D-scores from Acaster and colleagues (table 4 in original publication)

FEV1	**EQ-5D scores ± SD**
Severe<41%	0.552 ±0.29
Moderate 41-70%	0.695 ±0.26
Mild >70%	0.741 ±0.27
Average total sample	0.67 ±0.28

Utility estimated by utility equation or ppFEV1 strata approach

The model includes two approaches to estimate health utilities. Vertex has chosen to use a *utility equation* to achieve a continous estimation of utilities. NoMA accepts Vertex' choice of using a utility equation instead of the estimation based on $ppFEV_1$ strata. How utility is modelled, is an important issue as the ICER increases with more than 2 million NOK by switching from *equation-based* to *strata-based* utility estimation, for both populations (see sensitivity analysis in 4.2.3). Therefore NoMA considers it important to discuss the following limitations.

Vertex used a *utility equation* to predict SF-6D utilities in their base-case. The parameters chosen to predict health utilities are $ppFEV_1$ and a cumulative number of pulmonary exacerbations (PEx). This approach raised the following conceptual and empirical questions:

- *Are the predictors included in the utility equation appropriate?*
    - Vertex assumes that the main predictors of HRQoL for CF patients are the two physical effect measures of lung capacity (ppFEV1) and exacerbations. Solem et al (60, 61) provide evidence that pulmonary exacerbations, PE-related hospitalizations, and ppFEV1 were significant predictors of EQ-5D index and VAS. The impact of ppFEV1 was relatively smaller than PEs. Acaster and colleagues support that $ppFEV_1$ indeed varies with HRQoL

measured by CFQ-R and utility measured by EQ-5D (55). However, it remains intransparent for NoMA why Vertex choose (only) these parameters in the equation.

- *Are the two predictors used in the utility equation correlated?*
    - ppFEV$_1$ and PEx are two separate measures of lung function. It is likely that lung function measured by ppFEV$_1$ deteriorates with infections or other pulmonary exacerbations. This is shown in chapter 3.3.1. Infections with PA colonization predicts lower ppFEV$_1$, and a greater rate of decline in pulmonary function over time (51). Furthermore, the number of exacerbations may be linked to the overall lung function measured by ppFEV$_1$. The use of multivariable mixed model repeated measures regression analysis requires noncorrelated predictors. This assumption could not be assessed by NoMA as Vertex did not provide any information about multicollinearity and the size of standard errors of the predictors used in the regression analysis.

- *Are the included predictors sufficient to explain the variations in health utility?*
    - SF-6D is a generic, preference-based utility instrument that captures HRQoL on eight generic dimensions of health (physical functioning, role limitation- physical bodily pain, general health, vitality, social functioning, role limitations-emotional, mental health) (62). Hence, NoMA is concerned that the equation used to predict SF-6D utilities only includes physical lung parameters. NoMA has not received more detailed information about the proportion of explained variance (R^2) which made it impossible to assess how well the predictors explain the variation in health utilities.

With the information provided by Vertex, NoMA could not evaluate if the assumptions related to using multivariable mixed-model repeated measures regression analysis had been fulfilled, or even tested. Further, no empirical proof has been provided to what extent the utility equation provides a good fit for the SF-6D utilities observed in EVOLVE and EXPAND.

Utility increment

NoMA shares Vertex' concern that the utility values do not cover the entire disease burden of patients with CF. Both changes in *respiratory* and *non-respiratory* outcomes are likely to impact CF patients' HRQoL. Vertex assumes that the predictors used in the utility equation exclusively capture the impact of *respiratory* outcomes on health utilities. In order to represent the influence of *non-respiratory* outcomes on health utilities, a utility increment was added to the utility equation for patients who received TEZ/IVA.

NoMA thoroughly assessed the validity of this utility increment. We conclude that Vertex' arguments in favour of this increment are not convinving. NoMA bases this conclusion on the following issues:

i) The increment is based in EQ-5D utilities (55) and is added to the equation that is used to predict SF-6D utilities. NoMA is not aware of any evidence that supports the equivalence of EQ-5D and SF-6D utilities in the CF population that allowed to "mix" utilities that originate from two different instruments.

ii) The argument for including a utility increment relies upon an assumption that EQ-5D and SF-6D are equally insensitive in capturing utility gains in non respiratory domains in the CF population. This is not based on any empirical evidence.

iii) To explain the necessity of adding the non-respiratory utility increment, Vertex refers to Acaster and colleagues (55) who found that non-respiratory, domains in the CFQ-R questionnaire are significant predictors of the EQ-5D utility, while the respiratory domain is not a significant predictor. The authors hypothesise that this could be «due to the fact that the impact of respiratory symptoms is captured through functioning (non-respiratory) dimentions of the CFQ-R, which map onto the dimentions in the EQ-5D» (55). This indicates that the effect of respiratory and non-respiratory domains on quality of life are difficult to disentangle. There is a risk of double counting the utility gain if the effects of non-respiratory domains, estimated completely independently, are added to the utilities based on respiratory predictors only.

Overall, adding a non-respiratory utility increment estimated outside the core utility regression model is not statistically correct. Vertex has not provided an alternative method of including non respiratory predictors. Lastly, adding a constant non-respitatory utility increment based on an 8-week EXPAND trial to the lifetime time horizon is weakly substantiated.

Uncertainty in health utilities after lung transplantation

The post-transplantation utilities are difficult to validate since it is unknown if the utilities were collected from patients with CF or patients having lung-transplantation due to other diagnoses. Furthermore, it remains unclear if assuming the same utility for pre- and post- lung transplantation (0.81) is plausible. NoMA has accepted Vertex' assumptions.

Coverage of relevant factors that are not reflected in health utilities

The occurrence of adverse events and the time patients use for treatment are examples of factors that likely influence patients' HRQoL. Several studies showed that CF patients use a lot of time to follow their treatment schedule (59, 63, 64). In non-acute phases, patients use 1.5 hour on average per day on disease management, while in periods with infections the patients use up to 6 hours on average per day (65). However, time spent on treatment has not been taken into account in the documentation sent in by Vertex. This presumeably is a conservative approach as treatment with TEZ/IVA would likely relieve patients of acute phases. However, time spent on treatment included in the utility function would result in lower utility weights. As seen in scenario analysis with lower utility weights applied increase the ICER (4.2.3).

4 HEALTH ECONOMIC ANALYSES

This section presents a summary of the economic evidence submitted by Vertex in support of the use of TEZ/IVA for the treatment of patients ≥ 12 years with CF, and NoMA's assessment of the evidence. The

health economic model include the calculation of costs, life-years gained, and quality-adjusted-life-years (QALYs) gained.

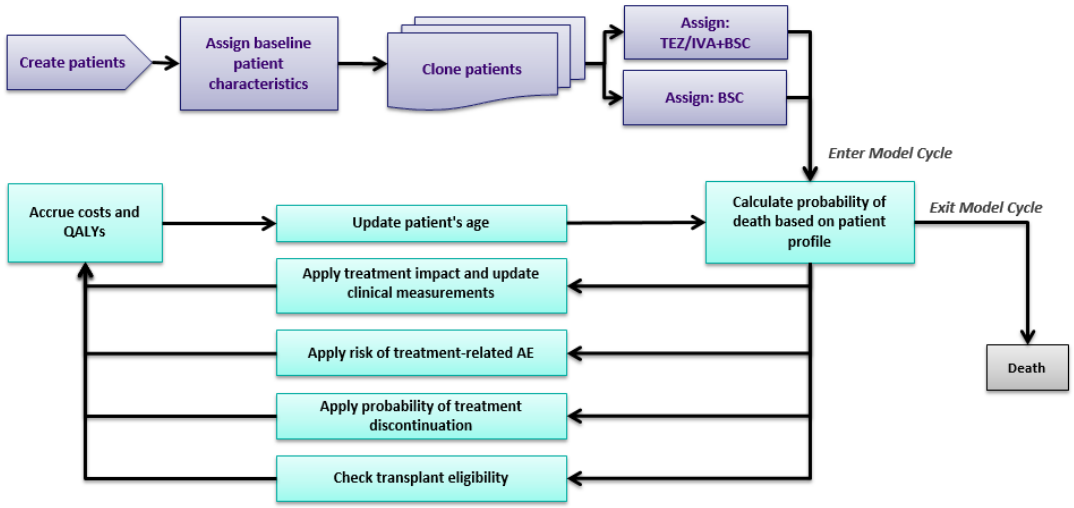
4.1 MODEL, METHOD AND ASSUMPTIONS

4.1.1 Model description

Vertex submitted an individual-patient state-transition model. Vertex used this type of model to account for patient heterogeneity with regard to F508-del mutation. This model type is recommended by NICE for use when patient heterogeneity can bias results on a cohort level (66). Patient-level simulation models estimate mean cost and benefits for a group of patients based on the costs and benefits of each individual in this group.

The purpose of the model is to track the progression and treatment impact for patients with CF over time and to assess the cost-effectiveness of TEZ/IVA in combination with BSC compared to BSC only.
The model can be run for the F/F population and the F/RF population separately. Figure 25 provides an overview of the model structure for the F/F population. When using the model for predicting outcomes for the F/RF population there is an additional option of selecting IVA+BSC as a comparator.
A sample of individual patients with predefined characteristics are drawn from the EVOLVE or EXPAND studies and are simulated through the model. An option of choosing a patient population based on the EVOLVE study or EVOLVE and Study 110 is available in the F/F model.

The patient profiles were duplicated in order to assign identical patients to the treatment arms. In total 2,000 patients were simulated and ran through the model. The only difference between the patients in the treatment arms is the assigned treatment.



AE, adverse event; BSC, best supportive care; QALY, quality-adjusted life-year; TEZ/IVA, tezacaftor/ivacaftor

Figure 25 Health economic model for F/F patients

The cycle length model is variable. One cycle lasts for four weeks during the first two years. Thereafter, a yearly cycle length is applied.

For each model cycle patients' age, $ppFEV_1$, weight-for-age z-score, the occurrence of pulmonary exacerbation, eligibility and occurrence of lung transplantation, development of diabetes, occurrence of adverse events and treatment discontinuation are updated. The risk of death is updated in accordance with the assigned patient characteristics in each model cycle.

The model provides estimates of mean LYs, QALYs, and costs per cohort, as well as incremental outcomes and ICERs. Clinical outcomes that the model reports include median predicted survival, mean time spent in $ppFEV_1$ states, cumulative change in $ppFEV_1$, annual pulmonary exacerbation rates, and proportion of patients receiving a lung transplant. In the model, it is assumed that 90% of the patients with ppFEV1 less than 30% undergo lung transplantation.

NoMA´s assessment

NoMA considers the choice of an individual-patient state-transition model as appropriate.

It is difficult to externally validate the model as very limited epidemiological data on particular CF genotypes are available. In particular, the annual decline in ppFEV1 per age as derived from the model could not be validated against existing registries as the data presentation is different (see chapter 3.3.1). Similarly, PEx projections per age could not be validated as genotype-specific literature that would present the data in a similar way could not be identified. This is viewed as a considerable limitation of this STA. Instead, NoMA has to rely on the input efficacy parameters of the model which are often highly uncertain (broad CI), and sourced from external studies of a short follow-up period (chapter 3.3.1). Furthermore, there is considerable uncertainty associated with the health utilities used in the model (see 3.3.3 for further discussion).

4.1.2 Analysis perspectives

The main analysis by Vertex is performed from a Norwegian extended healthcare perspective. In accordance with NoMA's guidelines, VAT has not been included in the analysis. Health outcomes include patients' life-years and HRQoL. Discounting of costs and effect is set to 4% per year. The model uses a monthly cycle length for the first two years and one year thereafter. The model uses a lifetime horizon.

NoMA´s assessment

The healthcare perspective is in accordance with NoMA's guidelines (67). The monthly cycle length is sufficient for reflecting short-term changes in costs and health states. The lifetime horizon is appropriate.

However, the extrapolation of treatment outcomes is based on clinical studies with very short follow-up time. This makes the extrapolation very uncertain.

Upon request by NoMA, Vertex has provided a new updated scenario with 3% discounting from year 40 and 2% from year 70, in line with NoMA's guidelines. This resulted in an 80 000 NOK lower ICER when compared to Vertex's main scenario. However, Vertex has not been able to implement this change in the main model. Consequently, NoMA could not implement the updated discount rate in its base-case.

4.1.3 Resource use and costs

Submitted documentation

The following cost components are considered in the model:

Drug price

The drug costs used in the model is the list price of TEZ/IVA for a pack of 28 doses. The same price is used for IVA for a pack of 28 doses (Table 23). Vertex has assumed that generic medications will be available for all CFTR modulators after 11 years, at which time a reduction in the cost of therapy by 58% in the first year and 88% in the subsequent years is modelled, based on the Norwegian stepped price model (68).

Table 23 Drug costs provided by Vertex, excl. VAT

Drug acquisition costs		
Cost per pack (PRP excl. VAT) TEZ-IVA and IVA	67,822	NOK AUP excl. VAT from legemiddelsök (SLV, 2018)
Doses per pack – TEZ-IVA	28	
Annual acquisition costs TEZ-IVA	884,711	Estimation
Reduction in therapy cost at generic entry	58% first year 88% subsequent years	Suthoff ED, et al. Journal of Medical Economics 2017; 1369-6998

The compliance with CFTR modulator therapies is assumed to be 80 %, as observed in a real-world setting. The real-world compliance to CFTR modulator therapies is based on the results of a retrospective cohort study conducted by Suthoff et al. (2016) (39). This pharmacoepidemiology study analysed the impact of IVA on health resource utilization through analysis of US claims data. The study found that among 79 patients diagnosed with CF and prescribed IVA between January 1, 2012 and July 31, 2014, the average medication possession ratio was 0.8. Vertex has assumed that the real-world compliance is similar among all CFTR modulator therapies; thus, a compliance of 80% is applied to the cost of all CFTR modulators after the initial trial period in the model. In the model (Vertex basecase) it is assumed that no patients discontinue TEZ/IVA treatment after 8 and 24 weeks.

Annual monitoring costs

The cost of liver function tests and ophthalmologist visits are applied to patients receiving CFTR modulators.

Pertinent monitoring requirements are specified in the SmPC (14). The tests include a liver function test for concentrations of aspartate transaminase (AST), alanine transaminase (ALT), and bilirubin at three, six, nine, and 12 months after CFTR modulators initiation, in addition to two ophthalmologist visits in the first year of initiation. In subsequent years, the only monitoring test performed is a liver function test (once annually). No additional physician visits are assumed to accompany the liver function tests since CF patients are routinely monitored on a quarterly basis.

The annual monitoring costs are summarised in Table 24.

Table 24 Annual monitoring costs

Annual monitoring costs		
1st year	3,100	Normaltariffen, 2017-2018: allmennlege 2ad, specialistlege 3ad, enkel blodpröve 1e (all costs x 2 according to NOMA´s unit-cost database.) The monitoring for the first year is assumed to consist of 2 visits to ophthalmologist and 4 liver function tests.
Subsequent years	430	Normaltariffen, 2017-2018: allmennlege 2ad, specialistlege 3ad, enkel blodpröve 1e (all costs x 2 according to NOMA´s unit-cost database.) the monitoring for subsequent years consists of 1 liver function test

Disease management costs

Vertex has applied disease management costs in the model as annual costs per ppFEV1 categories and as costs specifically related to pulmonary exacerbation (PEx) events.

Resource use data in the CF population from a chart review conducted in the UK were used. Data was retrospectively collected from 8 specialists CF UK centres and were based on 200 CF patients who were 6 years or older, had F/F genotype or carried the G551D mutation. Full 24-month data was extracted for each patient, including patient characteristics, pharmacotherapy, and healthcare resource use. The chart review has not been published.

Disease management costs were categorized as *not attributable or unrelated to pulmonary exacerbations* and reported separately as annual direct medical costs. The total annual non-pulmonary exacerbation-related direct medical costs are accrued per patient based on their lung function over the model horizon,

until death or lung transplantation occurs. The disease management cost model inputs are stratified by disease severity (ppFEV1 strata) assumed to be the same for both the F/F and the F/RF populations.

Costs for PEx requiring IV antibiotic and/or hospitalization are included and applied only when such an event occurs.

Costs were estimated by multiplying the mean resource use with respective unit costs and reported in 2018 Norwegian kroner (NOK). Direct medical costs were stratified by $ppFEV_1$ and inflated to 2018 NOK.

Table 25 Disease management costs

Disease management costs (non-PE-related) by $ppFEV_1$		
$ppFEV_1$ < 40	335,551.76	Ramagopalan S, et al. 2014 European Meeting at the Society for Medical Decision Making.(69) Vertex data on file, Health care resource use and cost burden of cystic fibrosis in the NHS. Inflated from 2010 to 2017 Validated by Norwegian clinical experts
$ppFEV_1$ 40 to 69	260,849.89	
$ppFEV_1$ 70+	170,606.14	
Cost per Exacerbation		
$ppFEV_1$ < 40	[redacted]	
$ppFEV_1$ 40 to 69	[redacted]	
$ppFEV_1$ 70+	[redacted]	

Lung transplantation costs

Lung transplantation costs are applied as the cost of the lung transplant procedure itself and annual costs thereafter, stratified by year post-lung transplant (Table 26). The cost of transplantation is a weighted average based on the 2016–2017 reference costs of elective hospitalizations, non-elective long stays, and non-elective short hospital stays for patients receiving lung transplantation in the UK (European Medicines Agency 2018). The costs associated with follow-up care are based on a study by Anyanwu et al. (2002) which reported costs for up to 15 years post-lung transplant in 1999. The average costs per year for all patients receiving lung transplant reported by Anyanwu et al. were adjusted to reflect costs only for patients still alive in the given year (57). Unit prices are based on the DRGs from Helsedirektoratet.

Vertex assumes that patients that reach a ppFEV1 of 30 are eligible for lung transplant based on an article by Kerem et al from 1990(70). According to a Vertex UK study, 90% of patients eligible for lung transplants receive this treatment. The survival of patients with lung transplants is derived from International Society for Heart and lung transplantation(71).

Table 26 Lung transplant procedure costs

Lung transplantation costs		
Transplant Procedure	1,034,002.48	Helsedirektoratet, 2018. Innsatsstyrt finansiering Lungetransplantasjon DRG: 459
First Year Follow-up	38,475.92	
Second Year Follow-up	25,751.60	
Third Year Follow-up	25,751.60	
Years 4–9 Follow-up (Annual)	25,751.60	
Years 10+ Follow-up (Annual)	25,751.60	

Adverse event costs

Vertex has applied an average cost of 2210 NOK to treat AEs for one patient in the TEZ/IVA cohort, and 1608 NOK in the BSC cohort. The table below shows the costs per event for the AEs that are included in the model for the F/F population.

Table 27 Adverse event costs

Adverse Event Cost (per event)

Event	Cost per event
Nasopharyngitis	kr 308,00
Diarrhoea	kr 77,00
Headache	kr 77,00
Nausea	kr 77,00
Sputum increase	kr 154,00

Vertex has not described the source for the reference costs.

NoMA´s assessment

Drug price

According to NoMA's guidelines the unit costs must normally be kept unchanged throughout the analysis period of the STA because of uncertainty about technological developments or market developments in the future. In line with our guidelines, NoMA does not accept the assumption of lower prices of TEZ/IVA and IVA after 11 years due to the introduction of generic pharmaceuticals.

A compliance rate of 0.8 is in line with the sales data of other CFTR modulators from the Norwegian Prescription Database (NorPD) and is, therefore, accepted. Discontinuation rate is discussed in section 3.3.3.

Disease management costs

Vertex has provided an annual unit price for the disease management costs. This is based on the UK chart study conducted by Vertex. The study is not published some details are presented in a poster provided by Vertex. We have limited information about the calculation of management costs, except the information in the poster: "Total annual costs were calculated through aggregated individual costs for each of: a) pharmacotherapy, b) hospitalizations, c) outpatient visits, d) surgeries, and f) diagnostics". According to Vertex, Norwegian clinical experts has validated the costs.

Vertex has not provided a systematic literature search to map the resource use of patients eligible for TEZ/IVA current indications, nor for CF patients in general. By hand search NoMA found an article by Van Gool et al from 2013 that studied lifetime healthcare costs of CF in Australia and conducted a systematic literature review to identify cost-of-illness studies (72). This is presented in the table below. Some of the articles found in the literature review are old and may be outdated.

Table 28 Annual treatment costs by year and country - from Van Gool et al (72)

Source	Study year	Study country	Patients (n)	Mean age (y)	Age range (y)	Mean annual cost* (US $)
Robson et al. [5]	1990	UK	119	21	16–44	21,533
Wildhagen et al. [6]	1991	The Netherlands	81	14	0–37	22,737
Ireys et al. [7]	1993	USA	204		0–18	20,147
Baumann et al. [8]	1996	Germany	138		0–18	33,039
Johnson et al. [9]	1996	Canada	303	18		8,148
Lieu et al. [10]	1996	USA	136	17	0–56	17,546
Heimeshoff et al. [11]	2004	Germany	212	20	0– adult	50,723
Horvais et al. [12]	2001	France	65			21,830
Eidt-Koch et al. [13]	2006	Germany	301			27,999
DeWitt et al. [14]	2008	USA	352	14.6	5– adult	40,037

* All originally reported national currencies converted to US $ at 2009 price levels applying OECD PPP conversion rates and using the CCEMG – EPPI-Centre Cost Converter (see http://eppi.ioe.ac.uk/costconversion/default.aspx); blank values, not stated.

Van Gool et al estimates show increased costs with worsened conditions. They conclude:

> "*Overall, the mean annual cost associated with CF management is US $15,571, with a 95% confidence interval range of US $15,032 to US $16,110. For health states combined, annual health*

care costs decline somewhat after age 2 years, then generally rise until patients reach their early thirties, then plateau at around US $20,000 to US $25,000 per year. Based on the standard errors reported in Table 8, the decrease in health care after age 2 years is statistically significant, as are the increases in the teenage years. The overall median health care cost is US $6,233 per year and ranges from US $2,269 for children aged 6 to 7 years to US $16,704 for 26- to 28-year-old patients. The difference between the mean and median statistics indicates that health care costs are highly skewed."

The annual costs provided by Van Gool et al are lower than the estimates from Vertex. This may be due to different unit costs and treatment strategies. Hence, we believe the estimates provided by Vertex seems reasonable for a Norwegian setting and accepts the cost estimates.

NoMA has explored the impact of different annual costs in sensitivity analyses and the impact on the ICER seems to be small.

Lung transplantation costs

NoMA accepts the unit costs used for lung transplantation.

In the model, Vertex has assumed that 90% of patients with ppFEV1 status less than 30% will undergo a lung transplant. According to Norwegian clinicians, the ppFEV1 status is only one of the parameters that is evaluated to determine if the patient is eligible for transplantation. The CF-patients undergo a total assessment of several relevant risk factors, in addition to donor availability. Only patients with life expectancy of less than two years are eligible for lung transplants. Hence, the model may predict a different proportion of lung transplants among CF patients than in the Norwegian clinical practice.

The model predicts survival rate of patients that undergo lung transplants from the The International Society for Heart and Lung Transplantation (73). Factors such as the presence of pan-resistant organisms in patients with CF and donor age may potentially impact mortality after lung transplant (74, 75). According to Norwegian clinicians, Norwegian patients have among the highest survival rates internationally after a lung transplant. Hence, the model may predict a shorter life expectancy after lung transplant than seen in the Norwegian clinical practice, but this is uncertain and has not been explored further.

In NoMA's opinion, the assumptions made by Vertex are a simplification of the number of lung transplants in the Norwegian clinical practice. However, as this has little impact on the ICER, NoMA has accepted the survival rate and resource use for lung transplantations.

Other cost inputs

Compared to general costs for BSC, lung transplantation and treatment with CFTR modulators, costs for monitoring and cost of AEs are relatively low.

According to a Norwegian clinician contacted by NoMA, the cost input included in the costs calculation is in line with the annual monitoring of CF patients in Norway. Ophthalmologist visits is not part of regular annual monitoring. These costs have limited impact on the ICER estimates. NoMA accepts these costs.

4.2 RESULTS

NoMA has identified multiple important limitations and uncertainties in the analysis that remained. NoMA considers the follow-up time in the pivotal trials too short to demonstrate a lasting effect compared to BSC, the input parameters were uncertain and often sourced from external trials, external validation of model outputs could not be conducted, the choice of the health-related quality of life instrument was not sufficiently justified, nor was the utility estimation approach. NoMA considers the estimated gain in overall and quality-adjusted survival for TEZ/IVA compared to BSC to be highly uncertain. Additional follow-up data is needed to evaluate the long-term outcomes with TEZ/IVA and reduce a large amount of uncertainty in the analysis.

4.2.1 Incremental cost-effectiveness ratios (ICER)

Results from Vertex's and NoMA's base-case analysis are presented for both the F/F and F/RF populations below.

Vertex's base-case is based on 96 weeks follow-up data that have been submitted to NoMA on 22nd of October 2019.

Vertex's base-case results for the F/F population:

	TEZ/IVA	BSC	Difference
Total costs	NOK 16 185 998	NOK 3 454 692	NOK 12 731 306
Total QALYs	10.97	8.01	2.96
Total life years	13.98	11.03	2.96
Incremental cost per QALY gained			**NOK 4 304 115**
Incremental cost per life year gained			NOK 4 304 971

Vertex's base-case results for the F/RF population:

	TEZ/IVA	BSC	Difference
Total costs	NOK 14 154 827	NOK 2 760 232	NOK 11 394 595
Total QALYs	9.39	6.44	2.95

Total life years	11.60	8.85	2.76
Incremental cost per QALY gained			**NOK 3 864 038**
Incremental cost per life year gained			NOK 4 134 676

On NoMA's request Vertex has submitted an updated calculation with altered discount rates (lowered rates after 40 years, ref NoMA guideline). This could not be adjusted directly in the submitted models. This change resulted in a reduced ICER of about 80 000 NOK (not reported in the tables above).

Changes applied by NoMA:

NoMA has estimated a cost-effectiveness ratio for TEZ/IVA compared to BSC. Multiple important limitations and uncertainties in the analyses were identified and remain unchanged in NoMAs base case. NoMA therefore considers the cost-effectiveness estimates to be highly uncertain. NoMA has made four changes to the Vertex's scenario:

- F/F patient population from the TEZ/IVA EVOLVE study, rather than both the EVOLVE study and the LUM/IVA studies TRAFFIC and TRANSPORT.
- TEZ/IVA and IVA drug prices kept unchanged throughout the analysis period, and not reduced due to the introduction of generic pharmaceuticals.
- Health related quality of life increment for patients in the TEZ/IVA arm compared to patients in the BSC arm not included.
- TEZ/IVA discontinuation rate of 13.5% based on 96 week follow-up data from Study 110 included.

NoMA's base-case, results for the F/F population:

	TEZ/IVA	BSC	Difference
Total costs	NOK 17 088 785	NOK 3 332 132	NOK 13 756 653
Total QALYs	9.40	7.76	1.63
Total life years	12.64	10.68	1.96
Incremental cost per QALY gained			**NOK 8 416 427**
Incremental cost per life year gained			NOK 7 008 588

NoMA's base-case, results for the F/RF population:

	TEZ/IVA	BSC	Difference
Total costs	NOK 16 054 145	NOK 2 760 232	NOK 13 293 912
Total QALYs	8.43	6.44	1.98
Total life years	11.07	8.85	2.23
Incremental cost per QALY gained			**NOK 6 699 338**
Incremental cost per life year gained			NOK 5 973 491

The use of patient population from the EVOLVE study, rather than EVOLVE+TT reduces the life expectancy and QALYs gained in both arms. This change has minor impact on the ICER calculation. The most influential changes to the Vertex's base-case are the drug price of TEZ/IVA and the removed utility increment.

4.2.2 Costs Analysis

The main cost driver are the drug prices. Treatment with TEZ/IVA results in reduced pulmonary exacerbations and lung transplants, and hence lower costs for these treatments. However, TEZ/IVA treatment results in higher total disease management costs, due to longer life and thereby longer treatment duration. The drug price consists of approximately 80% of total treatment costs of intervention.

Table 29 Treatment costs- lifelong horizon ((in NOK excl. VAT)

Outcome		TEZ/IVA+BSC	BSC	Incremental vs BSC
Drug		13 449 376	-	13 449 376
Direct Medical		3 639 408	3 332 132	307 276
	Pulmonary Exacerbations	583 818	769 876	- 186 058
	Disease Management (Non-Exacerbation Related)	2 965 208	2 338 866	626 342
	Lung Transplant	81 725	221 831	- 140 106
	Adverse Event Management	2 062	1 559	502
	Monitoring Tests	6 596	-	6 596
Total		17 088 785	3 332 132	13 756 653

4.2.3 Sensitivity and scenario analyses

NoMA has performed the following scenario analyses. The most important parameters seem to be the drug price and the modelled utility. The analysis shown is for the F/F and F/RF populations.

F/F population:

	Parameter	NoMA's base-case	Scenario analyses	ICER in scenario analyses (NOK)
	NoMA's scenarios (ITT population)	**See 4.2.2 for all changes**	**-**	**8 416 427**
1	ppFEV1 rate of decline in the BSC arm			6 121 668
2	Patient age	Patients ≥12 years, with mean age of 26 years.	Patients with age 12-18	8 104 804
3	Utility	Utility equation based on SF 12 (SF6D) from EVOLVE trial.	FEV1 strata approach	8 322 147
4	Utility	Utility equation based on SF 12 (SF6D) from EVOLVE trial	FEV1 strata approach with utility data from Acaster et al.	9 714 358
5	Utility	Utility equation based on SF 12 (SF6D) from EVOLVE trial, excluding increment add on	Utility equation based on SF 12 (SF6D) from EVOLVE trial, including increment add on of 0,043 to the equation	6 748 758
6	Compliance rate	Compliance rate of 80%	Compliance rate of 100%	10 221 127
7	Compliance rate	Compliance rate of 80%	Compliance rate of 60%	6 423 166
8	Disease management costs	Estimations by Vertex: ppFEV1 < 40: NOK 335 551 ppFEV1 40 to 69: NOK 260 849 ppFEV1 > 70:	2X estimations by Vertex	8 701 055

		NOK 170 606		
9	Disease management costs	Estimations by Vertex: ppFEV1 < 40: NOK 335 551 ppFEV1 40 to 69: NOK 260 849 ppFEV1 > 70: NOK 170 606	1/2X estimations by Vertex	8 132 692
10	Diabetes	18,9% prevalence of diabetes	No patients have diabetes	8 493 481
11	Discontinuation rate based on Study 110 (96 weeks follow-up)	13,5%	5%	8 020 231

F/RF population:

	Parameter	**NoMA's base-case**	**Scenario analyses**	**ICER in scenario analyses (NOK)**
	NoMA's scenarios (ITT population)	**See 4.2.2 for all changes**	**-**	**NOK 6 699 338**
1	ppFEV1 rate of decline in the BSC arm	Min Age / Max Age / Change in ppFEV$_1$: 6 / 12 / -0,80 13 / 17 / -0,57 18 / 24 / -1,85 25 / 100 / -1,06	Min Age / Max Age / Change in ppFEV$_1$: 6 / 12 / -0,64 13 / 17 / -0,46 18 / 24 / -1,48 25 / 100 / -0,85	7 385 110
2	Patient age	Patients ≥12 years, with mean age of 26 years.	Patients with age 12-18	7 392 693
3	Utility	Utility equation based on SF 12 (SF6D) from EVOLVE trial.	FEV1 strata approach	7 003 168
4	Utility	Utility equation based on SF 12 (SF6D) from EVOLVE trial	FEV1 strata approach from with utility data from Acaster with colleagues.	7 622 975
5	Utility	Utility equation based on SF 12 (SF6D) from EVOLVE trial, excluding increment add on	Utility equation based on SF 12 (SF6D) from EVOLVE trial, including increment add on of 0,043 to the equation	5 581 637

6	Compliance rate	Compliance rate of 80%	Compliance rate of 100%	8 307 153
7	Compliance rate	Compliance rate of 80%	Compliance rate of 60%	5 091 523
8	Disease management costs	Estimations by Vertex: ppFEV1 < 40 – NOK 335,551.76	2 X estimations by Vertex	6 867 374
9	Disease management costs	Estimations by Vertex: ppFEV1 < 40 – NOK 335,551.76	½ X estimations by Vertex	6 615 320
10	Diabetes prevalence	18,9% prevalence of diabetes	No patients have diabetes	6 824 843
11	Discontinuation rate based on Study 110 (96 weeks follow-up)	13,5%	5%	6 679 844

The model seems insensitive to changes in both a decline in the ppFEV1 rate and reduced treatment effect of TEZ/IVA. The most sensitive input data seems to be the compliance rate and the utility increment.

The compliance rate only affects the total costs of the treatment but not the modelled treatment effect of TEZ/IVA. It is reasonable to assume that the estimated effect size of TEZ/IVA is sensitive to the actual use of the drug. If the patients use TEZ/IVA according to the approved label (100% compliance rate) which reflects the effect input data of the model, the ICER increases substantially for both populations.

NoMA acknowledges that measuring utilities with a generic preference-based instrument is challenging in the CF population. The utility increment added to the TEZ/IVA arm impacts the ICER most considerably. In NoMA's opinion Vertex's assumptions about how to estimate utilities are weakly substantiated.

Utility weights used in the model for CF patients are high, and higher than would be expected for a severe disease as CF. The main driver of the utility gain is due to life years gained with TEZ/IVA treatment, instead of improved health-related quality of life. Scenario analysis using lower utility weights for more severe FEV1 health states increased the ICER. If treatment with TEZ/IVA was to delay worsening of FEV1 status, we would expect that this scenario analysis reduced, rather than increased the ICER.

4.3 NoMA´S CONCLUSION ON THE INCREMENTAL COST-EFFECTIVENESS RATIO (ICER)

NoMA has estimated an incremental cost-effectiveness ratio for tezacaftor/ivacaftor (TEZ/IVA) compared to Best Supportive Care (BSC). Multiple important limitations and uncertainties in the analysis were

identified and remained, and NoMA therefore considers the cost-effectiveness estimates to be highly uncertain.

In NoMA's base-case analyses, the additional costs for TEZ/IVA compared to BSC, with public list prices ex. VAT for medicines, are:

- 8.4 million NOK per QALY gained in the F/F population
- 6.7 million NOK per QALY gained in the F/RF population

NoMA's analysis does not take into account lower discount rates from year 40 and 70. In the Vertex scenario this resulted in an 80 000 NOK lower ICER. However, Vertex was not able to implement these discount rates in the main model. Consequently, NoMA could not implement the updated discount rate in our base-case.

5 BUDGET IMPACT ANALYSIS

The budget impact for year 1-5 after introduction is based on the assumption that the intervention will be recommended for use in clinical practice by the four regional health authorities and possibly implemented in the guidelines from the Directorate of Health. Two scenarios are considered:

A. The technology is recommended for use in clinical practice by the regional health authorities for the eligible patient population as described in this STA
B. The technology is not recommended for use in clinical practice

The budget impact is the difference between the budget impact in the two scenarios.

5.1 ESTIMATION OF THE NUMBER OF PATIENTS POTENTIALLY ELIGIBLE FOR TREATMENT

Clinical experts recruited by the regional health authorities have estimated that around 110 patients with CF and F/F genotype will be eligible for treatment with Symkevi (tezacaftor/ivacaftor) in combination with Kalydeco (ivacaftor) each year in Norway. Of these 110 patients, about 30 patients are receiving treatment with Orkambi (lumacaftor/ivacaftor), rf. Chapter 3.1. 30 patients with F/RF genotype will be eligible.

The number of patients expected to be treated in the first 5 years if Symekvi is recommended for use in clinical practice is presented in Table 30. The number of patients expected to be treated if Symekvi is not recommended is presented in Table 31.

The main assumptions in the Table 30 and Table 31:

- The number of eligible patients for Symkevi is stable. Thus, the number of potential new patients equals the number of patients no longer eligible due to disease severity or mortality. The expected life years in both treatment arms exceed 5 years.
- Compliance rate of 80% is used.
- All patients on treatment with Orkambi will switch to Symkevi. List prices are somewhat similar for Orkambi and Symkevi.
- Discontinuation rates from the studies EVOLVE/EXPAND and 110 are applied. In the models 14.3% and 8.1% of the patients discontinue TEZ/IVA treatment after 24 and 8 weeks (i.e. duration of the EVOLVE and EXPAND studies). During the 96 weeks long follow-up time13.5% discontinued TEZ/IVA. This gives the following mean discontinuation rates for each year, weighted with the number of F/F and F/RF respectively.

Year 1	Year 2	Year 3	Year 4	Year 5
17 %	7 %	3 %	0 %	0 %

Table 30 The number of patients expected to be treated with Symkevi (tezacaftor/ivacaftor) in combination with Kalydeco (ivacaftor) in the next 5 years – scenario where treatment is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Symkevi (tezacaftor/ivacaftor) in combination with Kalydeco (ivacaftor) and BSC	116	107	104	104	104
Orkambi (lumacaftor/ivacaftor) and BSC	0	0	0	0	0
Best supportive care (BSC) alone	24	33	36	36	36
Total	140	140	140	140	140

Table 31 The number of patients expected to be treated with Symkevi (tezacaftor/ivacaftor) in combination with Kalydeco (ivacaftor) in the next 5 years – scenario where treatment is not recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Symkevi (tezacaftor/ivacaftor) in combination with Kalydeco (ivacaftor) and BSC	0	0	0	0	0
Orkambi (lumakaftor/ivakaftor) and BSC	30	30	30	30	30
Best supportive care (BSC) alone	110	110	110	110	110
Total	140	140	140	140	140

5.2 COST ESTIMATES

NoMA has calculated the budget impact drug costs for Symkevi in combination with Kalydeco, Orkambi and BSC. All other costs are excluded. The main cost driver in the analysis is the drug price. Our analysis show that other treatment costs are almost similar for intervention and BSC. The cost difference between the arms are negligable in relation to drug price. Hence we have not included BSC costs in the budget impact calculation. We have used drug costs with a 80% compliance rate.

Drug costs have been calculated for the F/F and F/RF population.
Drug costs in NOK per patient per year after treatment initiation are presented in Table 32 (F/F).

Table 32 Drug costs per patient per year after treatment initiation. List price, including VAT and undiscounted.

	Year 1	Year 2	Year 3	Year 4	Year 5
Symkevi (TEZ/IVA) in combination with Kalydeco (IVA) and BSC	1 769 423	1 769 423	1 769 423	1 769 423	1 769 423
Orkambi (LUM/IVA) and BSC	1 482 190	1 482 190	1 482 190	1 482 190	1 482 190

BSC alone	0	0	0	0	0

5.3 BUDGET IMPACT

The estimated budget impact in NOK as a result of drug costs only for the eligible patient population is presented in Table 33.

Table 33 Estimated budget impact of drug costs for the eligible patient population. List price, including VAT and undiscounted, ITT population.

	Year 1	Year 2	Year 3	Year 4	Year 5
Symkevi (TEZ/IVA) recommended for use	204 638 145	189 673 980	184 186 983	184 186 983	184 186 983
Symkevi (TEZ/IVA) not recommended for use	44 465 692	44 465 692	44 465 692	44 465 692	44 465 692
Budget impact of recommendation	160 172 453	145 208 289	139 721 292	139 721 292	139 721 292

The budget impact of a positive recommendation for Symkevi in combination with Kalydeco for the eligible patient population as described in this STA is estimated to be around 140 million NOK including VAT in the fifth year after introduction. The calculations are uncertain and based on simplifications.

In this estimation of budget consequences of introducing Symkevi in combination with Kalydeco, NoMA has assumed that all CF patients with F/F and F/RF genotype are treated with Symkevi and does not consider market shares of Symkevi and other potential CFTR modulator treatments.

6 SUMMARY AND DISCUSSION

Health service interventions are evaluated against three prioritisation criteria – the benefit criterion, the resource criterion and the severity criterion. The priority-setting criteria are assessed and weighed against one another. The more severe the condition or the more extensive the benefit of the intervention, the more acceptable higher resource use will be. Quality and uncertainty associated with the documentation and the budget impact are included in the overall assessment of interventions.

NoMA has identified multiple important limitations and uncertainties in the analysis that remained. The trials were considered too short to be able to justify a lasting treatment effect over the time horizon, the input parameters were uncertain and often sourced from external trials, external validation of model outputs could not be conducted, the choice of the health-related quality of life instrument was not sufficiently justified, nor was the utility estimation approach. NoMA considers the estimated gain in overall and quality-adjusted survival for TEZ/IVA compared to BSC to be highly uncertain.

Additional follow-up data is needed to evaluate the long-term outcomes with TEZ/IVA and reduce a large amount of uncertainty in the analysis. NoMA welcomes the submitted follow-up data for 96 weeks (Study 110) that allows updating the treatment effect of TEZ/IVA. NoMA considers the two-year data to be too immature to reliably estimate the long-term effect of TEZ/IVA given the change in the long-term annual rate of ppFEV1 decline as observed in the Belgian and UK registries.

Drug costs and the way utility is modelled has the largest impact on the ICER.

- Throughout the models time horizon the size of relative effect is based on a 100% compliance rate. However, costs in the model correspond to an 80% compliance rate. This has considerable impact on the ICER.
- In Vertex base case it is assumed that no patients discontinue TEZ/IVA after 8 or 24 weeks.
- The monthly cost of TEZ/IVA is about 130 000 NOK ex VAT.
- Evaluating the internal and external validity of the utility estimates has been challenging.

NoMA's assessment of the benefit criterion:

CF is caused by mutations in the CFTR gene coding for epithelial chloride channels responsible for regulating salt and water absorption and secretion. The failure to regulate chloride transport in organs results in the multisystem pathology associated with CF. On group level patients with a double copy of F508del (F/F) are considered to have a severe illness with poor or lacking CFTR function. Patients with one copy of F508del and another mutation coding for residual function (F/RF) are considered to have a better CFTR function than F/F patients. The prognosis for *individual* CF patients varies with the patient's genotype and phenotype. The phenotypical expression (manifestation of CF) in the respiration system varies. TEZ/IVA is a CFTR modulator treatment for CF patients with F/F mutation, and 14 specific F/RF mutations.

The clinical efficacy and safety of TEZ/IVA was demonstrated in two phase 3 RCT's:

- F/F population: the 24 week EVOLVE study
- F/RF population: the 8 (+8) week cross-over study EXPAND

TEZ/IVA plus BSC is compared to placebo plus BSC in these trials. Patients from EVOLVE and EXPAND could also enter the open, one-armed follow-up trial Study 110.
All patients received TEZ/IVA in Study 110. All trials have now been completed. Final cut off data from follow-up Study 110 was received 22nd of October 2019.

The EVOLVE and EXPAND trials showed statistically significant changes in lung function (i.e. the primary endpoint ppFEV1) in favor of TEZ/IVA compared to BSC alone. Follow-up data from Study 110 shows that improvement in lung function is maintained for additional 96 weeks for patients with F/RF mutation. For patients with F/F mutation lung function improved compared to baseline. However, Study 110 lacks a comparator (BSC) arm and hence does not provide information about the relative effect.
A statistical significant improvement in rate for pulmonary exacerbations (PEx) was shown in favour of TEZ/IVA in the EVOLVE study (F/F population). PEx was an explorative endpoint in the EXPAND study (F/RF population) and hence results from this study are descriptive only; a positive trend for improvement in PEx rate was shown for TEZ/IVA. After 96 additional weeks of treatment in Study 110 the trend was positive for PEx rate in both F/F and F/RF populations.

Efficacy and safety of TEZ/IVA is demonstrated for patients ≥ 12 years in the TEZ/IVA studies. The studies are considered relevant for Norwegian clinical practice. Taking into account that the treatment of CF is lifelong, and that EMA (4) recommends a minimum of 12 months study duration for FEV1 endpoints for therapies aiming to slow or stop pulmonary disease progression, NoMA considers the follow-up time in the pivotal trials too short to be able to demonstrate a lasting effect compared to BSC.

Utility weights used in the model for CF patients are high, and somewhat higher than would be expected for a severe disease like CF. The main driver of the utility gain is due to life years gained with TEZ/IVA treatment, instead of improved health-related quality of life. Scenario analysis using lower utility weights for more severe FEV1 health states increased the ICER.

NoMA's assessment of the resource criterion:

The analyses considered the following cost components:

- Drug price
- Annual monitoring costs
- Disease management costs
- Lung transplantation costs
- Adverse event costs

The main difference between TEZ/IVA treatment and BSC is drug costs. Other treatment costs are comparable. Treatment with TEZ/IVA does not reduce other health care costs. The mean total healthcare cost was approximately 16 million NOK (excl. VAT) per patient for this CFTR modulator regimen for F/F and 14 million NOK (excl. VAT) for F/RF patients.

NoMA's assessment of the severity criterion:

The current prognosis for patients with CF is poor. In Norway, the degree of severity affects whether the costs are considered reasonable relative to the benefit of the treatment. NoMA has estimated that patients ≥12 years with CF have an absolute shortfall of approximately 30 and 28 Quality Adjusted Life Years (QALYs) for respectively the F/F and F/RF populations.

NoMA's assessment of budget impact:

NoMA estimated the budget impact for the specialist health services to be around 140 million NOK including VAT in the fifth year after introduction if all eligible adult patients with CF and F/F or F/RF genotype are treated with TEZ/IVA.

Norwegian Medicines Agency, 07-02-2020

Elisabeth Bryn (e.f.)

Assessors

Einar Andreassen
Reidun Os Husteli
Yvonne Anne Michel
Ania Urbaniak

APPENDIX 1 SEVERITY AND SHORTFALL

NoMA has quantified the severity of cystic fibrosis using absolute shortfall, calculations are made for both F/F and F/RF populations. Absolute shortfall is the number of future quality-adjusted life years (QALYs) an average patient in the patient group will lose because of his/her disease, compared to the average in the population of the same age. Absolute shortfall is the same as the reduction in expected future QALYs without the treatment under consideration.

The calculation of absolute shortfall is done in stages:

1) The mean age at start of treatment for the relevant Norwegian patient group which is being considered for the new treatment is defined. We refer to the age as A. The TEZ/IVA trials included patients >12 years. The *mean* age in the modelled cohorts was 26.8 years for F/F patients and 35.6 years for F/RF patients (the cohorts also included patients >12 years). The mean age in the Norwegian Registry for F/F and F/RF patients >12 years was higher than in the TEZ/IVA trials with respective 30.1 years and 56.5 years. As discussed in chapter 3.1, the age 30,1 years is used for the F/F population and age 35,6 years is used for the F/RF population when calculating AS.
2) The number of remaining QALYs (undiscounted) for an average person from the general population with the age A is estimated. We refer to this as $QALYs_A$. We use mortality data for the Norwegian population from Statistics Norway (76) in calculating expected remaining lifetime at different ages. This is combined with age-specific quality of life data to calculate quality adjusted remaining lifetime for different ages. Pending reliable Norwegian figures, we use Swedish age-specific quality of life data, with value sets based on UK general population available for EQ-5D, based on Sun et al (77) and Burstrøm et al (78). See Table 34 below.
3) The prognosis for the relevant Norwegian patient group is calculated. The prognosis is the average number of remaining QALYs (undiscounted) for the patient group with the current standard treatment. We refer to this as P_A. We calculate the prognosis from the number of QALYs the patients can expect with the comparator treatment in the health economic analysis.
4) The absolute shortfall (AS) is the difference between the estimated number of remaining QALYs for the general population at the same age (point 2) and the expected number of remaining QALYs for the patient group with the comparator treatment (point 3).
5) Absolute shortfall (AS) = $QALYs_A - P_A$

Table 34 Calculation of severity F/F

Age	A	30,1
Expected $QALYs_A$ without disease (undiscounted)	$QALYs_A$	43,1
Expected number of $QALYs_A$ with disease (undiscounted)	P_A	12,7
Number of lost QALYs with disease (absolute shortfall)	AS	30,4

Table 35 Calculation of severity F/RF

Age	A	35,6
Expected $QALYs_A$ without disease (undiscounted)	$QALYs_A$	38,0
Expected number of $QALYs_A$ with disease (undiscounted)	P_A	9,8
Number of lost QALYs with disease (absolute shortfall)	AS	28,2

NoMA estimates the absolute shortfall based on current standard care to be approximately 30 QALYs for the F/F population and 28 QALYs for the R/RF population.

Expected remaining QALYs in the general population

Table 36 shows the expected remaining QALYs and health state utility values (HSUV) respectively, by age for the general population. Expected remaining QALYs are based on mortality data for the Norwegian population from Statistics Norway (76) and the age-specific HSUV in the right-hand column.

Pending reliable Norwegian figures, the HSUV from two Swedish studies have been used (77, 78). In the studies, Swedish age-specific quality of life data is combined with British population-based EQ-5D value-setting tariffs (79). Pending reliable Norwegian figures, the HSUV from two Swedish studies have been used (77, 78). In the studies, Swedish age-specific quality of life data is combined with British population-based EQ-5D value-setting tariffs (79).

HSUV for the age group 21-73 years are taken from Sun et al (77), which is the most recent of the two Swedish studies and has the greatest number of respondents. In this publication, HSUV for other age groups are not presented. For the age group 0-20 years, we have assumed that HSUV are somewhat higher than for the age group 20-33 years. We have set it at 0.89.

In order to obtain fairly even age ranges, we have established an age group 74-88 years based on data from Burstrøm et al (78).(78). For this group, we have calculated a simplified weighted average which gives a HSUV of 0.76 (rounded). The calculation is based on the following: For the age group 74-79 years we assume a HSUV at 0.79 based on Burstrøm et al. For the age group 80-88 years we use a HSUV of 0.74 from Burstrøm et al.

This gives a drop from 0.80 to 0.76 from the age group 55-73 years to the age group 74-88 years. We assume a corresponding (relative) drop from the age group 74-88 years to the last age group 89-105 years, to which we give a HSUV of 0.72.

Table 36 Expected remaining QALYs and HSUV in the general population

Age	Expected remaining QALYs	HSUV	Age	Expected remaining QALYs	HSUV	Age	Expected remaining QALYs	HSUV
0	69,1	0,89	36	38,0	0,85	72	11,3	0,8
1	68,3	0,89	37	37,2	0,85	73	10,7	0,8
2	67,5	0,89	38	36,3	0,85	74	10,1	0,76

3	66,6	0,89	39	35,5	0,85	75	9,5	0,76
4	65,7	0,89	40	34,7	0,85	76	9,0	0,76
5	64,8	0,89	41	33,8	0,85	77	8,5	0,76
6	63,9	0,89	42	33,0	0,85	78	8,0	0,76
7	63,1	0,89	43	32,2	0,85	79	7,5	0,76
8	62,2	0,89	44	31,4	0,85	80	7,0	0,76
9	61,3	0,89	45	30,6	0,82	81	6,5	0,76
10	60,4	0,89	46	29,8	0,82	82	6,1	0,76
11	59,5	0,89	47	29,0	0,82	83	5,6	0,76
12	58,6	0,89	48	28,2	0,82	84	5,2	0,76
13	57,7	0,89	49	27,4	0,82	85	4,8	0,76
14	56,8	0,89	50	26,7	0,82	86	4,4	0,76
15	56,0	0,89	51	25,9	0,82	87	4,1	0,76
16	55,1	0,89	52	25,1	0,82	88	3,7	0,76
17	54,2	0,89	53	24,4	0,82	89	3,4	0,72
18	53,3	0,89	54	23,6	0,82	90	3,1	0,72
19	52,4	0,89	55	22,9	0,8	91	2,9	0,72
20	51,6	0,89	56	22,1	0,8	92	2,7	0,72
21	50,7	0,87	57	21,4	0,8	93	2,5	0,72
22	49,9	0,87	58	20,7	0,8	94	2,3	0,72
23	49,0	0,87	59	20,0	0,8	95	2,1	0,72
24	48,2	0,87	60	19,3	0,8	96	2,0	0,72
25	47,3	0,87	61	18,6	0,8	97	1,9	0,72
26	46,5	0,87	62	17,9	0,8	98	1,8	0,72
27	45,6	0,87	63	17,2	0,8	99	1,6	0,72
28	44,8	0,87	64	16,5	0,8	100	1,5	0,72
29	43,9	0,87	65	15,8	0,8	101	1,5	0,72
30	43,1	0,87	66	15,1	0,8	102	1,5	0,72
31	42,2	0,87	67	14,5	0,8	103	1,3	0,72
32	41,4	0,87	68	13,8	0,8	104	1,1	0,72
33	40,5	0,87	69	13,2	0,8	105	0,8	0,72
34	39,7	0,87	70	12,5	0,8			
35	38,8	0,85	71	11,9	0,8			

APPENDIX 2 COMMENTS FROM VERTEX

Introduction

Vertex Pharmaceuticals (Vertex) would like to thank the Norwegian Medicines Agency (NoMA) for the comprehensive report provided on our dossier regarding Symkevi + Kalydeco for treatment of Cystic Fibrosis (CF) (ID 2018_112). We would also like to provide some comments and additional inputs on the received single technology assessment report (STA-report), information we believe will be of importance to the upcoming finalization of the assessment.

As described in the report, CF is a severe, genetic disease leading to pre-mature mortality and morbidity. Until the relatively recent approval of CFTR modulators, which treat the underlying cause of the disease, the only treatments available for CF patients were symptomatic. The launch of the new class of medicines, including Symkevi + Kalydeco, has meant a significant step-change in the treatment of CF.

An initial reflection on the appropriateness of the assessment methodology

Health Technology Assessment (HTA) of rare diseases in general and CF in particular, applying traditional cost-effectiveness methods, has proven to be extremely challenging. Vertex believes that the methodology applied by most HTA-bodies, such as NoMA, is not appropriate for valuing these kinds of transformative medicines. The main reason is that the method has inherent biases against innovative medicines, such as CFTR modulators, developed and intended for lifelong chronic conditions where the health benefits are accrued far in the future. There are two key elements we would like to emphasize and ask NoMA to consider in the second reading of the STA-report on Symkevi + Kalydeco:

Price decreases over time. Norway has a well-defined system for pricing of generic copies. We believe this method should be applied in this case as the treatment in question is a tablet. Applying no price decrease following generic entry should, in our opinion, be considered the least likely and realistic future scenario. In our opinion a more plausible option would include an even greater decrease in prices than the one Vertex has suggested.

Discounting at same rate for costs and health benefits. The second reason why the current method is problematic in this situation is related to the discount rate and the asymmetry in the timing of cost versus benefits of the treatment. The full product costs are accrued from day 1 while the benefits in the form of increased survival or quality of life (QoL) are not fully realized until years or decades later. A methodology, such as the one used in the report, will influence the ICER denominator heavily. Vertex would therefore like to suggest that NoMA use a more flexible approach when discounting the costs and benefits for treatments aiming to help patients with lifelong chronic conditions such as CF.

More specific comments to the Symkevi + Kalydeco report

Vertex is pleased to see that NoMA has accepted most of the assumptions made in the application although there may be too much attention paid to what may be called “uncertainties”. CF is a rare disease, meaning that inherently there will be limitations regarding data. While all HTA involves uncertainty to some degree, we strongly believe that all assumptions made are robust and based on best data or science available.

It is possible to change parameters in a way that cost-effectiveness outcome becomes worse, but this is equally true in the other direction. Making reasonable, positive changes to modelling assumptions can easily decrease the ICER by more than 50%. The idea with modelling is to represent reality as best

possible; Vertex would argue that such a positive scenario is a better mirror of reality than the base case presented by NoMA.

Vertex would also like to highlight and clarify the following related to the NoMA assessment. Please see our comments in the report for complete input.

EMA guidelines. The EMA guidelines from 2008 regarding clinical development of products for treatment of cystic fibrosis is referred to in several sections of the report. However, in 2016 EMA deemed these to be outdated (https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-need-revision-guideline-clinical-development-medicinal-products-treatment-cystic/ewp/9147/2008-revision-1_en.pdf) for several reasons, e.g. related to new drug classes and recent clinical trial experience. This update has not yet been published.

Residual function mutations. The clinical presentation and progression of CF can vary with genotype: patients with residual function (RF) mutations typically have later onset of disease than those who carry two copies of the F508del-CFTR mutation (Zielenski, 2000); however, they still suffer from early mortality due to severe, progressive lung disease (Davis et al, 2004).

Choice of sample size. Regarding the choice of sample size (EVOLVE only or EVOLVE + Traffic/Transport). In order to derive the simulated cohort, the model randomly samples 2,000 profiles with replacement from the pool of available risk profiles. A larger pool of patients therefore increases the robustness of the analysis and the results. If NoMA choses to base the analysis on a smaller set of patients, i.e. EVOLVE only, that will decrease the robustness of the analysis.

Utility increment. Assigning utility scores based only on $ppFEV_1$ and PEx would be measuring quality of life only in terms of respiratory function and would not consider benefits on other organ systems. In addition, this is still conservative considering no effect on caregiver burden is included in the model.

Discontinuation rate. The rate of discontinuation observed in the 110 study due to Treatment Emergent Adverse Events is also further justification for why the rate of discontinuation assumption should be considered as 0 beyond the trial period. In this study the rate of discontinuation due to TEAEs was 2.1%.

Concluding remarks

Vertex has followed the Norwegian health care debate closely over the past few years. During 2019, we have noticed the public debate changing regarding the introduction of new pharmaceuticals. In particular, we've been closely following concerns related to access to rare disease medicines and the critique of their assessment.

In December, the Norwegian Parliament recommended, with a specific reference to rare diseases like CF, an evaluation of the system for introducing new methods in the hospital sector (i.e. Nye Metoder). Vertex believes that our suggestions above for the current evaluation of Symkevi + Kalydeco could be a valuable contribution for the upcoming review. We fear that unless these and similar changes are implemented in the system the accessibility to new treatments for Norwegian patients with rare diseases will be severely hampered.

Vertex is not only an innovator when it comes to the research and development of new treatments for cystic fibrosis. We also have a proven track record for being creative when it comes to developing new and

mutually beneficial procurement agreements for our medicines. One of the most recent agreement was made with the Danish health care system. Thanks to this new way of looking at procurement Danish CF-patients will have full access to all our CFTR modulators shortly after receiving European market authorization. There are also examples with creative solutions from HTA markets like England, Australia and Scotland.

Our willingness to discuss new models for procurement was also noticed when the Norwegian parliament recently debated the whitepaper on the future of the Health Industry in Norway. We are looking forward to the upcoming negotiations with Sykehusinnkjøp regarding our CFTR modulators.

REFERENCES

1. Norsk barnelegeforening. Pediatriveiledere. 714 Cystisk fibrose, 2018.
2. Colombo C. et al. The implementation of standards of care in Europe: State of the art. Journal of Cystic Fibrosis. 2011;10:S7-S15.
3. Norsk senter for cystisk fibrose. Anbefalinger for rutinemessig kontroll og oppfølging av pasienter med cystisk fibrose i Norge - arbeidsgruppens anbefalinger. 2011.
4. EMA. GUIDELINE ON THE CLINICAL DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF CYSTIC FIBROSIS. 2009.
5. Nasjonalt medisinsk kvalitetsregister for cystisk fibrose. Årsrapport 2017.
6. Zolin A. et al. ECFSPR Annual Report 2017. 2019.
7. Haugen T. B. Pasienter med cystisk fibrose lever lenger enn før. Tidsskr Nor Legeforen. 2014;134(2138).
8. EMA. Public Assessment Report for Symkevi. 2018.
9. Castellani C. et al. ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis. 2018;17:153-78.
10. legemiddelhåndbok N. T10.8 Cystisk fibrose. 2016.
11. Geborek A. Hjelte L. Association between genotype and pulmonary phenotype in cystic fibrosis patients with severe mutations. Journal of Cystic Fibrosis. 2011;10:187-92.
12. Brennan M.-L. and Schrijver I. A Review of Associated Phenotypes, Use of Molecular Diagnostic Approaches, Genetic Characteristics, Progress, and Dilemmas. J Mol Diagn. 2016;18(1):3-14.
13. Southern KW et al. Correctors (specific therapies for class II CFTRmutations) for cystic fibrosis. Cochrane Database of Systematic Reviews. 2018;8.
14. EMA. Preparatomtale for Symkevi. 2018.
15. EMA. Preparatomtale for Kalydeco. 2017.
16. EMA. Summary of Product Characteristics for Orkambi. 2018.
17. NorPD. ATC/DDD for R07AX02 and R07AX30, years 2017 and 2018. 2019.
18. Statens Legemiddelverk. Retningslinjer for dokumentasjonsgrunnlag for hurtig metodevurdering av legemidler. 2018.
19. Cystic Fibrosis Foundation. UK CF Registry Annual Data Report 2008. 2009.
20. NICE. Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation. Technology appraisal guidance [TA398]2016.
21. EMA. Concept paper on the need for revision of the guideline on the clinical development of medicinal products for the treatment of cystic fibrosis (CHMP/EWP/9147/08). 2016.
22. Taylor-Cousar J. L. et al. Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. N Engl J Med. 2017;377(21):2013-23.

23. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. N Engl J Med. 2015;373(3):220-31.
24. EMA. Orphan Maintenance Assessment Report. Kalydeco (N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide) Treatment of cystic fibrosis EU/3/08/556 (EMEA/OD/010/08). 2018.
25. Rowe S. M et al. Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. N Engl J Med. 2017;377(21):2024-35.
26. McKone E. F. et al. CFTR Genotype as a Predictor of Prognosis in Cystic Fibrosis. Chest Journal. 2006;130:1441-7.
27. Norsk senter for cystisk fibrose ved E. Bakkeheim. Tabell over alder norske CF-pasienter. 2019.
28. Suthoff E. D. et al. Healthcare resource utilization associated with ivacaftor use in patients with cystic fibrosis. Journal of Medical Economic. 2016;19(9):845-51.
29. Ishak KJ, Kreif N, Benedict A, Muszbek N. Overview of parametric survival analysis for health-economic applications. PharmacoEconomics. 2013;31(8):663-75.
30. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.
31. Liou T. G. et al. Predictive 5-Year Survivorship Model of Cystic Fibrosis. Am J Epidemiol. 2001;153(4):345-52.
32. Adler AI, Shine BS, Chamnan P, Haworth CS, Bilton D. Genetic determinants and epidemiology of cystic fibrosis-related diabetes: results from a British cohort of children and adults. Diabetes care. 2008;31(9):1789-94.
33. Konstan M, McKone E, Moss RB, Johnson C, Lubarsky B, Suthoff E, et al. Rate of Lung Function Decline in Patients with Cystic Fibrosis (CF) Having a Residual Function Gene Mutation. B108 CYSTIC FIBROSIS, PRIMARY CILIARY DYSKINESIA, AND ILD. p. A4847-A.
34. 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. The Lancet Respiratory medicine. 2017;5(2):107-18.
35. 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. American journal of respiratory and critical care medicine. 2015;192(7):836-42.
36. Goss CH, Burns JL. Exacerbations in cystic fibrosis. 1: Epidemiology and pathogenesis. Thorax. 2007;62(4):360-7.
37. 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 technology assessment (Winchester, England). 2014;18(18):1-106.
38. Flume PA, Owen CA, Brown CD, Wang L, Jain M, Yuan ZJ, et al. Long-term Safety and Efficacy of Tezacaftor/Ivacaftor in Patients With Cystic Fibrosis Homozygous for F508del-CFTR or Heterozygous for F508del and a Residual Function Mutation: First Interim Analysis Results of a Phase 3, Open-label, Rollover Study. D23 ADULT CF AND NON-CF BRONCHIECTASIS. American Thoracic Society International Conference Abstracts: American Thoracic Society; 2018. p. A7807-A.

39. 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. Journal of medical economics. 2016;19(9):845-51.
40. International guidelines for the selection of lung transplant candidates. The American Society for Transplant Physicians (ASTP)/American Thoracic Society(ATS)/European Respiratory Society(ERS)/International Society for Heart and Lung Transplantation(ISHLT). American journal of respiratory and critical care medicine. 1998;158(1):335-9.
41. Clinical guideline 9: transplant assessment. Clinical Guidelines: Care of children with cystic fibrosis.: Royal Brompton & Harefield, N. H. S. F. T.; 2011 [Available from: http://www.rbht.nhs.uk/healthprofessionals/clinical-departments/cystic-fibrosis/clinical-cf-guidelines-care-of-children/.
42. Adult Lung Transplantation Statistics.: The International Society for Heart and Lung Transplantation.; 2016 [Available from: https://ishltregistries.org/registries/slides.asp.
43. Liou TG, Adler FR, FitzSimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. American journal of epidemiology. 2001;153(4):345-52.
44. Cystic Fibrosis Foundation. UK CF Registry Annual Data Report 2016. 2016.
45. Cystic Fibrosis Foundation. US Patient Registry 2011 Annual Data Report. Bethesda, Maryland. 2012.
46. Cystic Fibrosis Foundation. UK Cystic Fibrosis Registry Annual Data Report 2012. September. 2013.
47. Cystic Fibrosis Foundation. Annual Data Report. 2017 Patient Registry. 2017.
48. Trust CF. UK Cystic Fibrosis Registry 2017- Annual Data Report. 2017.
49. Stephenson AL, Tom M, Berthiaume Y, Singer LG, Aaron SD, Whitmore GA, et al. A contemporary survival analysis of individuals with cystic fibrosis: a cohort study. European Respiratory Journal. 2015;45(3):670-9.
50. Keogh RH, Szczesniak R, Taylor-Robinson D, Bilton D. Up-to-date and projected estimates of survival for people with cystic fibrosis using baseline characteristics: A longitudinal study using UK patient registry data. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2018;17(2):218-27.
51. McCarthy C OCO, Franciosi A , McElvaney N. Factors Affecting Prognosis and Prediction of Outcome in Cystic Fibrosis Lung Disease. INTECH. 2015.
52. Sawicki GS, Konstan M, McKone E, Moss RB, Johnson C, Lubarsky B, et al. Rate of Lung Function Decline in Patients with Cystic Fibrosis (CF) Having a Residual Function Gene Mutation. B108 CYSTIC FIBROSIS, PRIMARY CILIARY DYSKINESIA, AND ILD. American Thoracic Society International Conference Abstracts: American Thoracic Society; 2017. p. A4847-A.
53. (BMR-RBM-BCFR) TBCFR. Annual Report. 2016.
54. Sawicki GS, McKone EF, Millar SJ, Pasta DJ, Konstan MW, Lubarsky B, et al. Patients with Cystic Fibrosis and a G551D or Homozygous F508del Mutation: Similar Lung Function Decline. American journal of respiratory and critical care medicine. 2017;195(12):1673-6.
55. Acaster S, Pinder B, Mukuria C, Copans AJH, outcomes qol. Mapping the EQ-5D index from the cystic fibrosis questionnaire-revised using multiple modelling approaches. 2015;13(1):33.
56. Anyanwu A, McGuire A, Rogers C, Murday AJT. Assessment of quality of life in lung transplantation using a simple generic tool: Presented at the 19th Annual Meeting of the International Society of Heart and Lung Transplantation in San Francisco, April 1999. 2001;56(3):218-22.

57. Anyanwu AC, McGuire A, Rogers CA, Murday AJTJot, surgery c. An economic evaluation of lung transplantation. 2002;123(3):411-20.
58. 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. 2014.
59. Congleton J, Hodson M, Duncan-Skingle FJT. Quality of life in adults with cystic fibrosis. 1996;51(9):936-40.
60. Solem C, LLonch MV, Liu S, Botteman M, Lasch K, Rodriguez S, et al. Responsiveness of the EQ-5D Index and Visual Analog Scale to changes in lung function in patients with cystic fibrosis. Value in Health. 2014;17(3):A178.
61. Solem CT, Vera-Llonch M, Liu S, Botteman M, Castiglione B. Impact of pulmonary exacerbations and lung function on generic health-related quality of life in patients with cystic fibrosis. Health and quality of life outcomes. 2016;14(1):63.
62. Brazier JE, Roberts JJMc. The estimation of a preference-based measure of health from the SF-12. 2004:851-9.
63. Briesacher BA, Quittner AL, Fouayzi H, Zhang J, Swensen AJPp. Nationwide trends in the medical care costs of privately insured patients with cystic fibrosis (CF), 2001–2007. 2011;46(8):770-6.
64. Quittner AL, Sawicki GS, McMullen A, Rasouliyan L, Pasta DJ, Yegin A, et al. Psychometric evaluation of the Cystic Fibrosis Questionnaire-Revised in a national sample. 2012;21(7):1267-78.
65. fibrose Nffc. https://www.cfnorge.no/behandling/tidsbruk-behandlingsrutiner/ 2019 [
66. Davis S, Stevenson M, Tappenden P, Wailoo AJRBDSU. NICE DSU Technical support document 15: Cost-effectiveness modelling using patient-level simulation. 2014.
67. Norwegian Medicines Agency. Guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals. 2018.
68. Norwegian medicines agency. Trinnpris på legemidler 2019 [Available from: https://legemiddelverket.no/offentlig-finansiering/trinnpris.
69. Sreeram Ramagopalan DL, Jamie L. Rubin, Andrew P. Cox, Sharon MacLachlan,. Predictors of healthcare costs for cystic fibrosis patients in the United Kingdom. the15th Biennial European Meeting at the Society for Medical Decision Making. Belgium2014.
70. Kerem E, Corey M, Kerem B-s, Rommens J, Markiewicz D, Levison H, et al. The relation between genotype and phenotype in cystic fibrosis—analysis of the most common mutation (ΔF508). New England Journal of Medicine. 1990;323(22):1517-22.
71. International Society of Heart and Lung Transplants. Adult lung transplant statistics 2017 [Available from: https://ishltregistries.org/registries/slides.asp?year=2017.
72. Van Gool K, Norman R, Delatycki MB, Hall J, Massie J. Understanding the costs of care for cystic fibrosis: an analysis by age and health state. Value in health. 2013;16(2):345-55.
73. The international Society for heart and lung transplantation. 2016 [Available from: https://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry.
74. Lay C. et al. Outcomes in cystic fibrosis lung transplant recipients infected with organisms labeled as pan-resistant: An ISHLT Registry–based analysis. J Heart Lung Transplant. 2019;38(5):545-52.
75. Auråen H. et al. Effect of Donor Age on Outcome of Lung Transplantation Stratified by Recipient Diagnosis: A Nordic Multicenter Study. Transplantation. 2019;103(4):807-14.
76. Whitehurst DG, Bryan S, Lewis MJMDM. Systematic review and empirical comparison of contemporaneous EQ-5D and SF-6D group mean scores. 2011;31(6):E34-E44.

77. Sun S, Irestig R, Burström B, Beijer U, Burström K. Health-related quality of life (EQ-5D) among homeless persons compared to a general population sample in Stockholm County, 2006. Scandinavian journal of public health. 2012;40(2):115-25.
78. Burström K, Johannesson M, Diderichsen F. Swedish population health-related quality of life results using the EQ-5D. Quality of life research. 2001;10(7):621-35.
79. Dolan P. Modeling valuations for EuroQol health states. Medical care. 1997:1095-108.